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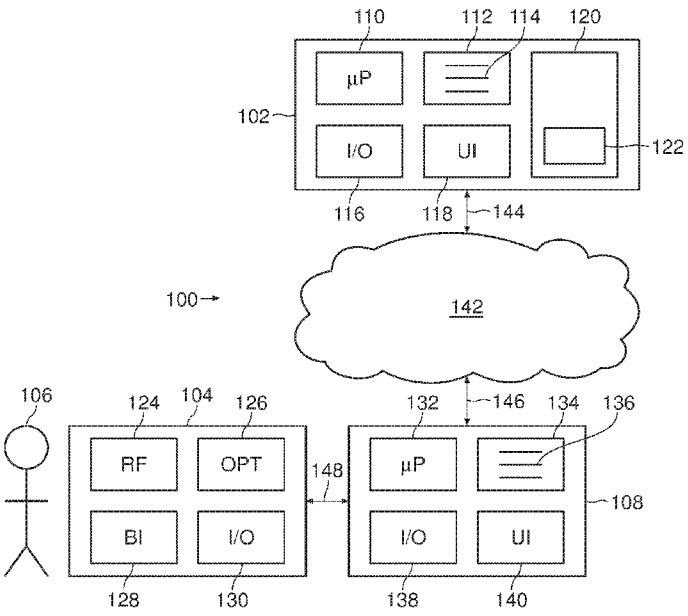

FIG. 1

(57) Abstract: A server apparatus (102) for monitoring blood glucose in a wearer (106) of a wearable device (104) is configured to perform the first mode of operation of blood glucose monitoring for the wearer of the device using data obtained by a radio- frequency blood glucose monitoring module (124) in the wearable device. The server apparatus is also configured to perform a second mode of operation of blood glucose monitoring using data obtained by a light spectroscopy blood glucose monitoring module (126) in the wearable device. The server apparatus performs a threshold comparison between a reference blood glucose value for the wearer of the device and the threshold glucose value (314). A first one of the first mode of operation and the second mode of operation is selected in dependence of the threshold comparison.

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SERVER APPARATUS AND WEARABLE DEVICE FOR BLOOD GLUCOSE MONITORING AND ASSOCIATED METHODS

The invention relates to a server apparatus for monitoring blood glucose in a wearer of a wearable device. The invention also relates to a wearable device for blood glucose monitoring. The invention also relates to a computing device for communicating information between a wearable device and a server apparatus for monitoring blood glucose. The invention also relates to a method of operation of the server apparatus. The invention also relates to a method of operation of the wearable device. The invention also relates to a method of operation of the computing device. The invention also relates to a computer program product and/or a computer program for implementing the methods.

The invention has particular, but not exclusive, application for ongoing – for example, continuous – non-invasive blood glucose monitoring for the wearer of the wearable device. When the term "continuous" is used herein, this may mean ongoing monitoring where data is gathered and/or transmitted for processing on a non-stop basis. Additionally or alternatively, this may mean data is gathered and/or transmitted for processing in batches at discrete intervals of, for example, between one and 15 minutes. Such time intervals may be specified by a clinician. Implementation of the techniques disclosed herein may allow for accurate non-invasive self-blood glucose monitoring. Further, the techniques disclosed herein may allow for ongoing monitoring with minimal calibration.

Diabetes Mellitus (DM) is increasing worldwide at an unprecedented pace. The International Diabetes Federation (IDF) estimates an upsurge from 382 million diabetics in 2013 to 592 million diabetics by 2030. The World Health Organisation has declared it as a global epidemic. The annual cost with diabetes management will increase from an approximate $376 billion in 2013 to $490 billion in 2030. The management of DM involves strict glycaemic control with a target HbA1c of 7% to

reduce complications. Self-monitoring of blood glucose and self-knowledge of daily blood glucose increases compliance to medications and lifestyle measures and higher chances of achieving a target HbA1c. Self-monitoring of blood glucose is also important in patients with type 1 diabetes who are at high risk of hypoglycaemia unawareness so that appropriate action can be taken on time. The normal blood glucose concentrations are in the range of 4-8 mmol/L whereas pathophysiological blood glucose concentrations are in the range of 2-30 mmol/L in patients with DM.

Currently monitoring of blood glucose concentrations is mainly done by self-monitoring blood glucose (SMBG) systems which involves the users pricking their fingers for each estimation. Continuous glucose monitoring systems (CGMS) are also used to monitor blood glucose especially for patients on insulin pumps. Almost all SMBG systems uses a cost effective electrochemical biosensor and they suggest automatic lancet devices to prick the fingers to obtain the blood samples which can be painful as patients with DM require to monitor blood sugars very frequently up to 4-7 times daily. The CGMS system although minimally invasive suffers from limitations in terms of discomfort to patients, the requirement for continuous calibration and high susceptibility to biofouling. Current techniques for self-blood glucose monitoring tend to be invasive, painful and high cost.

CGMS was introduced as a minimal invasive solution, utilizing interstitial fluid (ISF) to estimate blood glucose (BG) values. This invasive technology is widely accepted and extensively used by type 1 and type 2 diabetics to continuously monitor their blood glucose levels on a daily basis.

Figure 14 shows a sensor-measuring glucose in the interstitial fluid. Micro-dialysis based approaches undergo an additional delay to extract ISF

Currently, most CGMS devices on the market are invasive. An in-vivo method comprising of enzymatic sensors--inserted subcutaneously in the abdomen or an ex-

vivo method by means of micro dialysis fluid extraction to the ex-vivo enzymatic sensor can be used [1].

Calibration of the interstitial sensor signals to the capillary blood glucose samples via a blood glucose meter is still required. For Example, Dexcom's commercial device "Seven" requires an average twice per day calibration for the subcutaneous sensors seven-day lifetime [2]. Currently, all CGMS systems require calibration with blood glucose measurement after insertion and recalibration thereafter in regular intervals [3]. This process of calibration has to be repeated every time a new sensor is replaced (every 2-7 days).

CGM devices exhibit time delays when compared to capillary blood glucose. Short delays dependent on the membrane thickness are due to transit time effects due to diffusion through a glucose membrane. Micro-dialysis based approaches undergo an additional delay to extract ISF.

Furthermore, subcutaneous enzymatic sensor signal is typically in the nano-ampere range, where the current magnitude is proportional to ISF glucose. Additional filtering to smooth any electronic noise and artefacts is necessary, hence, creating a delay that is proportional to the amount of smoothing required. In total, three stages digital filtering comprising of moving average filter, nonlinear or linear rate limiting filter and data smoothing decimation filter is required. After which the multi-minute sensor signal is sent for calibration. The total system delay reported by commercial invasive CGM products during steady-state operation is from 5 minutes to 12.6 minutes. The current CGMS systems are extremely costly with the sensor cost dominating the long term.

Another non-invasive method uses an ultrasonic sensor. The acoustic velocity (c) in fluids and soft tissue depends on the compressibility (β), which is determined by the

intermolecular bonding forces, and the density (ρ) of the medium, according to the following equation:

$c=(\beta*\rho)1/2.$

Breaking the water structure by hydrogen bonding of the glucose molecules causes a less-bonded water to form a closer-packed and less compressible structure, Hence, glucose concentration changes in the extracellular fluid affect both density and adiabatic compressibility and therefore directly affect the acoustic velocity by a linear relationship. This effect can be measured by ultrasonic transceiver [10].

Recently there has been some interest in using fluids such as saliva [4], sweat and tears [5]. However these are dependent on the secretion on glucose in these fluids and may be accurate at higher concentrations. Additionally, there may be a lag time of up to 30 minutes. Although these may be good screening tools for hyperglycaemia, they do not give accurate quantitative measures of glucose in real time for all ranges.

Prior Art Blood glucose monitoring techniques and the devices developed including the limitations are summarized in Table 1.

Table 1: Shows various CGMS techniques along with their strengths and limitation.

Technique used	**Mechanism of Action**	**Device**	**Strengths**	**Limitations**
Reverse Iontophoresis	An electric potential causes Na^+, Cl^- anions to drift towards anode and cathode. Uncharged glucose in ISF is deposited and measured at cathode.	GlucoWatch (USA) (wrist – skin)	1.Non-invasive 2.CE and FDA approved 3. Includes temperature, perspiration and data software analysis.	1.Sensor Lag time with warm up time of 3 hours 2.Limited by sweating, movement, exercise and cannot be used in water. 3.Skin irritation 4. Works better at high glucose levels and does not reliably detect hypoglycemia.

Technique used	Mechanism of Action	Device	Strengths	Limitations
Bioimpedance spectroscopy	The changes in the glucose concentration of plasma change the membrane potential of red blood cells (RBCs) by varying their Na+ and K+ ion concentration. The changes in RBCs membrane potential are then determined by the impedance spectrum.	Pendra© (wrist-skin)	1.CE approved; 2.Software Data analysis, long battery life; alerts for rapid changes in glucose concentration and hypoglycemia. 3.Changes in impedance due to variations in temperature	1.Glucose readings vary in different individuals. 2.Requires additional calibration for differences in skin and underlying tissues among individuals; difficulty in calibration; 3.Pendra tape needs to be changed every 24 h; device needs to be reattached at the same spot where it was calibrated followed by 1 h equilibrium time; 4.Poor correlation of only 35% with glucose meters; Clarke EGA indicated 4.3% readings in error zone E; 5.Patient must rest for 60 min for equilibration before the reading; it cannot be used in many subjects whose skin types and basic skin impedances are unsuitable for the device; and, 6.Poor accuracy in post-marketing validation study.
Ultrasonic, Electromagnetic and heat capacity		Glucotrack (Earlobe skin)	1. High precision and accuracy as it employs various NGM techniques; 2. Calibration is valid for 1 month; 3. Alerts for hypo- and hyper glycaemia, 4.High accuracy in clinical trials;	1.Requires individual calibration against invasive basal and post-prandial blood glucose references before it can be used for glucose measurements; needs improvements in calibration procedure and algorithm for data processing. 2.Not marketed yet
Occlusion NIR spectroscopy		OrSense NBM-200G	1.CE approved; 2.Allows non-invasive measurement of glucose as well as hemoglobin	1.Bulky instrument not suited for home use. 2.Not marketed yet. Only used for educational and market awareness purposes.

Technique used	Mechanism of Action	Device	Strengths	Limitations
			and oxygen saturation. 3. Measures glucose continuously for 24 h without requiring frequent calibration. 4. Good accuracy in clinical trials.	
Laser microporation		SpectRx Inc. (Guided Therapeutics, Inc.)-skin	1. Uses invasive technique for measuring ISF glucose conc. 2. Good correlation with blood glucose in clinical trial.	1.Requires daily calibration with a blood glucose meter. 2.Lag time in ISF measuring tech. 3. ISF collecting device needs to be fixed to skin and replaced every 3 days. 4. Requires vacuum pump.
Transdermal		Prelude® SkinPrep System	1.Sensor warm up period of 1hr. 2.Wireless Glucose measurement every minute 3. Good accuracy in clinical trials.	1.Requires skin permeation 2. Skin irritation reported. 3. No hypoglycaemic alerts. 2. Not marketed yet.

The invention is defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

Implementation of the techniques described herein may offer significant technical advantages. For instance, a wearable device as described herein implements two different sensor technologies, which may have different ranges of optimal operation. One of the technologies may be selected for ongoing monitoring so that blood

glucose monitoring can be effected in the most accurate, efficient and convenient way possible for the wearer of the wearable device. Further, as the blood glucose values vary over time, this can be tracked more accurately and switching from one sensor technology to the other can be effected if the blood glucose values vary sufficiently.

Monitoring of the blood glucose values may be effected at a server, thereby minimising the processing burden on the wearable device itself, allowing simplification of the device as much as possible. The wearer of the device may be able to use a program to interface between the wearable device and the server apparatus, with the programme being an executable program such as those used in personal computers and the like, or an app for use in a smart device, such as a smart phone, a tablet or a smart watch.

The system described herein is particularly suitable for fine tuning using data obtained over a period of time. In one example, the wearable device and the server apparatus are configured to have their settings varied based on a machine learning algorithm which may be used to track the wearer's data and fine tune various system settings, such as switching thresholds and alarm conditions. One such example of threshold and alarm conditions relating to monitoring for a hypoglycaemic event. For instance, while it is unlikely the setting at which an alarm condition is triggered would be changed, it may be that the level at which alert (e.g. a condition which needs to be alerted to the user, but not yet as serious as an alarm condition) are set can be varied by the user, preferably with input from a consulting physician, perhaps taking into consideration the user's medication regime and/or any changes thereto.

Thus, self-monitoring of capillary blood glucose and continuous glucose monitoring systems provide a necessary tool for people suffering from diabetes to monitor their glucose level to guide therapeutic and lifestyle/behaviour measures which can

significantly lower HbA1c levels. Due to the invasive nature, frequent sensor replacement, multiple daily calibrations and time lag in reporting actual blood glucose values, the a non-invasive (NI) low cost solution as described herein provides a dire unmet need. A multisensor methodology and algorithmic approach that combines light spectroscopy, dielectric spectroscopy and machine learning is described herein. Other correction parameters from pulse oximetry, Heart rate, Body Mass Index (BMI) (fat percentage at the site of measurement), temperature, exercise and food are included into the system via mobile/computer OS application.

Further potential advantages include:

1. Improvement of signal to noise ratio and sensitivity. Implementation of the techniques disclosed herein may allow parallel monitoring using multiple sensors and parameters to maximize the signal to noise ratio.

2. Wearable systems with continuous glucose measurements. In one exemplary system, by using a waterproof thin flex cable, the hermetic sensor patch approximately can be attached to a smart watch for continuous measurement without degrading SNR. Some alternate measurement sites included but not restricted are ear (lobe)/ear canal, arm, foot, etc.

3. Precision in measurement of blood glucose concentration. Multiple methods with different correlation coefficients may be utilised to detect and predict hypo/hyperglycaemic events. One exemplary non-invasive continuous glucose monitoring system has its own proprietary algorithm and evaluated on the Clarke/Parkes error grid for ISO15197 standard.

4. Reducing the time taken for glucose measurement and reducing the lag time. The disclosed systems may not require multiple filtering stages as compared to known commercial continuous glucose monitoring systems. It may be possible to

determine real time blood glucose hence minimising lag time caused by filtering when compared to interstitial fluid sensors. The techniques disclosed can be implemented without detection using interstitial fluid analysis and, in these instances, there may be no physiological lead/lag when compared to measurement techniques requiring sampling of blood using finger pricking techniques.

Potential commercial applications include a non-invasive blood glucose meter. This could be, for example, integrated with an artificial pancreas to inject insulin into the body on an automatic basis. Abnormalities in body parameters through continuous multisensory data analysis may be detected. For instance, by implementing one or more RF techniques as disclosed herein and, with some refinement of the algorithm(s) discussed, from analysis of data trends, from appropriate sensor placement (e.g. on the user's neck) it may be possible to detect hypo/hyper thyroidism.

The invention will be described, by way of example only, and with reference to the accompanying drawings in which:

Figure 1 is a block schematic diagram illustrating an exemplary system for monitoring blood glucose in a wearer of a wearable device;
Figure 2 is a block schematic diagram illustrating an exemplary wearable device for monitoring blood glucose in a wearer of the wearable device;
Figure 3 is a series of blood glucose measurement diagrams;
Figure 4 is an architecture diagram illustrating system components;
Figure 5 is a series of layout diagrams illustrating an exemplary wearable device for monitoring blood glucose in a wearer of the wearable device;
Figure 6 is a diagram illustrating an exemplary method of wearing the wearable device of Figure 5;
Figure 7 is a graph illustrating a series of curves of relative permittivity versus frequency for six exemplary types of body tissue;

Figure 8 is a graph illustrating a radar sweep for an exemplary radio-frequency blood glucose monitoring module;

Figure 9 is a graph illustrating a series of blood glucose measurement values implementing the current non-invasive techniques compared with invasive techniques using a finger pricking technique;

Figure 10 is a second graph illustrating the series of blood glucose measurement values of Figure 9 as time series values;

Figure 11 is a Clarke Error Grid of the results from Figure 10;

Figure 12 is a series of Clarke Error Grids of historical blood glucose data obtained using a light spectroscopy technique;

Figure 13 is a schematic diagram for the overall operation of a blood glucose monitoring system implementing a multi-sensor approach; and

Figure 14 is a schematic layout diagram illustrating a known CGM sensor for measuring glucose in the interstitial fluid.

Referring first to Figure 1, an exemplary system for monitoring blood glucose in a wearer of a wearable device is illustrated. The system 100 comprises a server apparatus 102 for monitoring blood glucose. Server apparatus 102 is configured to process data obtained by wearable device 104, worn by wearer 106, relating to blood glucose levels of the wearer. In this example, server apparatus 102 communicates with the wearable device 104 through the wearer's computing device 108.

Server apparatus 102 comprises microprocessor 110, a memory 112 (e.g. a volatile memory such as a RAM) for the loading of executable instructions 114, the executable instructions defining the functionality the server apparatus 102 carries out under control of the processor 110. Server apparatus 102 also comprises an input/output module 116 allowing server apparatus 102 to communicate with other devices. User interface 118 is provided for user interaction and may comprise, for example, computing peripheral devices such as display monitors, computer

keyboards and the like. Server 102 comprises a data storage 120 for storing, for example, a database 122 of data relating to wearer 106 and, for example, historical blood glucose data and/or other sensor data.

Wearable device 104 comprises, principally, a radio-frequency blood glucose monitoring module 124 and a light spectroscopy blood glucose monitoring module 126. Wearable device 104 may also comprise a bio impedance sensor module 128 (depending on the system requirements) and an input/output module 130 allowing wearable device 104 to communicate with other devices. Wearable device 104 may have other components such as a microcontroller and a flash memory, but these are omitted from this figure for the sake of clarity.

In one example, the radio high-frequency blood glucose monitoring module 124 is configured for operation in the frequency range of 24 GHz to 24.25 GHz. It has been found that operation in this frequency range is particularly beneficial for a number of technical reasons. First, the depth of penetration in a user's skin area is greater when compared to the next ISM band of 61 to 61.5 GHz. Also, this is of course a short wavelength, and does not cause any damage to skin, or at the cellular level. The RF signal related to variations in blood glucose, is highly correlated as the RF signals can penetrate the cellular level where the cellular membrane permittivity changes can be measured with respect to changes in the blood glucose concentration. At the 24 GHz ISM band, an observable drop in the permittivity for different layers can be observed; see, for example, Figure 7. In this race, changes in blood glucose only effect the permittivity of blood, and this can be measured through the techniques described herein.

As described below with reference to Figure 5, exemplary wearable devices may have a flex cable installed. In at least one of these arrangements, the flex cable is required to transmit and receive this high-frequency 24 GHz signal, so the dielectric layer between the conductive flex layers has to be extremely low to reduce losses at

board level. From a cost and manufacturing perspective, it is extremely costly and difficult to achieve high yield high-frequency flex boards. Further, the ISM band of 61 GHz exhibits high losses in human tissue, and may be absorbed by the atmosphere, by water and the like. Additionally, for high-volume production, the integrated chips are manufactured utilising special low transistor node technologies, implementing for example, a silicon germanium process with high ft (unity gain current frequency) in order to implement mm wave (61 GHz ISM band) circuits. Operation in this frequency range allows realisation benefit from a manufacturing perspective. In the example of Figure 5 (described in more detail below) referring to the flex cable

Computing device 108 comprises a microprocessor 132, a memory 134 (e.g. a volatile memory such as a RAM) for the loading of executable instructions 136, the executable instructions defining the functionality the computing device 108 carries out under control of the processor 132. Computing device 102 also comprises an input/output module 138 allowing the computing device 108 to communicate with other devices. User interface 140 is provided for user interaction and may comprise, for example, computing peripheral devices such as display monitors, computer keyboards and the like. If the computing device 108 is, say, a smart phone, tablet device or smart watch, the user interface 140 is likely in the form of a touch panel display as is prevalent in many smart phone and other handheld devices.

Server apparatus 102 is configured for communications through communications network 142 (e.g. the Internet) and communications channel 144, which may be a wired or a wireless link, or a combination of both. Computing device 106 is configured for communications through communications network 142 and communications channel 146, which may be a wired or wireless link, or a combination of both. Wearable device 104 is configured for communications with computing device 108 through communications channel 148, which may be a wired or a wireless link, or a combination of both. In one implementation, communications channel 148 is a Bluetooth (TM) channel, with both wearable device 104 and wearer

computing device 108 having associated hardware and software therefor. Direct cable connections using, for example, a USB protocol, are also contemplated. In one respect, a cable connection may offer the advantage that any battery in the wearable device (omitted from Figure 1 for the sake of clarity) may also be charged through the cable connection. Additionally or alternatively, wearable device 104 is configured to communicate through another communications channel (not shown) through communications network 142 with server apparatus 102. That is, these communications are not routed through computing device 108. In such an arrangement, a headless router server, akin to an Internet router with an additional software stack, can be used to transmit data or receive data from a Bluetooth communication chip using the IPv4 or IPv6 software stack running on the Bluetooth chip. This allows communication directly to the server without using a mobile device or a smart device to act as a medium for data transmission and receiving.

Server apparatus 102 may be a single server as illustrated schematically in Figure 1, or have the functionality described above distributed across separate servers, and each of the separate servers may have its own hardware components corresponding to those illustrated in Figure 1. References herein to “a microprocessor”, “a memory” and the like are not necessarily to be considered limiting as applying to one and only one microprocessor operating in one and only one server apparatus, unless this is specifically stated.

Figure 2 provides a more detailed block diagram of the wearable device 104. Figure 2 illustrates again the radio-frequency blood glucose monitoring module 124, the light spectroscopy blood glucose monitoring module 126, the bio impedance sensor module 128 and the input/output module 130. The interface between the input/output module 130 and communications channel 148 is also illustrated.

In the example of Figure 2, wearable device 104 also comprises a power management module 200 and a controller unit 202, such as a micro control unit

which controls the operation of the wearable device 104. Other types of controller are also envisaged, including, for example, programmable logic controllers. Signal conditioning block 203 provides gain and filtering functionality for data received from one or more of modules 124, 126, 128 prior to conversion by analogue to digital converter 204.

Radio-frequency module 124 communicates with one or more antennas (not shown in Figure 2, but refer to Figure 4) on line 206. Light spectroscopy module 126 communicates with and/or powers a light source (not shown in Figure 2, but refer to Figure 4) on line(s) 208. Light spectroscopy module 126 communicates with and/or powers a photosensor (not shown in Figure 2, but refer to Figure 4) on line(s) 210. Suitable photosensors include one or more from Silicon, Silicone Germanium, Indium Gallium Arsenite, Gallium Phosphite, Germanium, and quantum dots. Bio impedance sensor module 128 communicates with and/or powers a first set of bio impedance sensors/sensor electrodes (not shown in Figure 2, but refer to Figure 4) on line(s) 212. Bio impedance sensor module 128 communicates with and/or powers a second set of bio impedance sensors/sensor electrodes (not shown in Figure 2, but refer to Figure 4) on line(s) 214.

Concerning radio-frequency blood glucose monitoring module 124, in one example, this implements a dielectric spectroscopy sensing technique which measures the permittivity of the wearer's body – or a part thereof – with respect to change in blood glucose concentration at a given frequency. This technique can be implemented to measure the glucose level in the wearer, for example at a localised site of measurement i.e. wrist or finger or skin flap between index finger and thumb, etc. Other suitable measurement sites include, for example, the earlobe.

It has been shown in separate studies that the permittivity of erythrocytes/Red Blood Cells increases linearly with an increase in the glucose concentration up to 20mmol/L approximately [8]. This shift in permittivity can be measured at RF/mm

wave frequency using, for example, dielectric spectroscopy techniques. Thus, the impedance and tissue radio wave signals can be used to sense changes in blood glucose concentration.

As mentioned above, Figure 3 is a series of blood glucose measurement diagrams. Turning first to Figure 3(a), this illustrates a first range 300 of operation across a first range of blood glucose values for the radio-frequency blood glucose monitoring module 124. In the example of Figure 3, first range 300 corresponds with a range of optimal operation of the radio-frequency blood glucose monitoring module 124 from a lower blood glucose value 302 to an upper blood glucose value 304. In one example, lower blood glucose value 302 is 0 mg/dL. In one example, upper blood glucose value 304 is 360 mg/dL. Range 300 represents a range of operation of the radio-frequency blood glucose sensor module in which the module's response is at least generally linear, therefore providing acceptable measurement results.

In Figure 3 (b) there is illustrated a second range 306 of operation across a second range of blood glucose values for the light spectroscopy blood glucose monitoring module 126. In the example of Figure 3, second range 306 corresponds with a range of optimal operation of the light spectroscopy blood glucose monitoring module 126 from a lower blood glucose value 308 to an upper blood glucose value 310. In one example, lower blood glucose value 308 is 36 mg/dL. In another example, lower blood glucose value 308 is 72 mg/dL. In one example, upper blood glucose value 304 is 500 mg/dL. Range 306 represents a range of operation of the light spectroscopy blood glucose sensor module in which the module's response is at least generally linear, therefore providing acceptable measurement results.

As illustrated in Figure 3(c), the first and second ranges 300, 306 have a range of overlap 312 – from lower value 308 of second range 306 up to upper value 304 of the first range 300 – in which both sensor modules 124, 126 exhibit acceptably linear performance.

An initial reference blood glucose value for the wearer of device 104 is taken from an invasive finger prick blood glucose test, and communicated to server apparatus 102. In one implementation, the initial reference blood glucose value is entered by the wearer at computing device 108 and communicated therefrom to server apparatus 102.

Additionally or alternatively, the initial reference blood glucose value may be transmitted automatically and/or directly to the server from, for example, a non-Bluetooth blood glucose meter. In such a way, it is not necessary for the user to enter the results into computing device 108. The initial finger prick value may be communicated directly from the wearable device (assuming it has a suitable transmitter) or it may be transmitted automatically to a computing device such as computing device 108. In one example, a customised device is provided to acquire the finger prick value and to communicate this to a computing device, such as computing device 108. The customised device may be a Bluetooth enabled custom printed circuit board which can be connected to any non-Bluetooth blood glucose meter, and the finger prick data to be used for the initial and daily calibration transmitted to computing device 108 using the Bluetooth protocol. This obviates the requirement for the user to enter the finger prick value, and may enable the non-invasive wearable sensor and the blood glucose meter seamlessly synchronising their system timings to define the precise moment of calibration data. The customised device may run one or more protocols depending on the model of the blood glucose meter in order to extract the finger prick value from the meter.

Server apparatus 102 initially sets a threshold blood glucose value 314 as illustrated in Figure 3(c). In the example of Figure 3, the threshold blood glucose value is set at 300 mg/dL, although other values are also contemplated where appropriate. As can be seen, the initial threshold blood glucose value lies in the range of overlap 312.

In the range of overlap 312, there may be a sub-range 316 of blood glucose values lower than the threshold blood glucose value 314 and a sub-range 318 of blood glucose values higher than the threshold blood glucose value 314.

Server apparatus 102 is configured to compare the initial reference blood glucose value with the threshold blood glucose value 314 and, therefrom, determine which of the radio-frequency blood glucose monitoring module 124 and the light spectroscopy blood glucose monitoring module 126 is best suited to performing ongoing (e.g. continuous) blood glucose monitoring in the environs of the reference glucose value. For example, it may be that the initial reference blood glucose value is a value lower than lower value 308 of the second range of operation 306 of the light spectroscopy blood glucose monitoring module 126, thereby indicating that radio-frequency blood glucose monitoring module 124 will exhibit more accurate performance than light spectroscopy blood glucose monitoring module 126 for blood glucose values of that order. Thereafter, ongoing non-invasive blood glucose monitoring may be conducted by server apparatus 102 using the measurement data obtained by radio-frequency blood glucose monitoring module 124.

In the event that the initial reference blood glucose value is a value higher than upper value 304 of the first range of operation 300 of the radio-frequency blood glucose monitoring module 124, this indicates that light spectroscopy blood glucose monitoring module 126 will exhibit more accurate performance than radio-frequency blood glucose monitoring module 124 for blood glucose values of that order. Thereafter, ongoing non-invasive blood glucose monitoring may be conducted by server apparatus 102 using the measurement data obtained by light spectroscopy blood glucose monitoring module 126.

In instances where the initial reference blood glucose value is in the range of overlap, either of the RF or light spectroscopy techniques can be selected for the initial ongoing monitoring, as long as the selected technique is acceptably linear in

that range of operation. For example, the initial reading yields a blood glucose value of 200 mg/dL and the light spectroscopy sensor data is selected initially for ongoing monitoring. In such a circumstance, the pathophysiological rate limited for glucose change per minute is known. If blood glucose concentration increases or decreases, the predicted output from the sensor changes accordingly. Thereafter, if the sensed blood glucose value approaches or crosses the threshold, the RF sensor data is then selected for ongoing monitoring.

More broadly speaking, server apparatus 102 may perform the selection simply on the basis of the initial reference blood glucose value being in the first sub-range 316 – thus indicating that the radio-frequency blood glucose monitoring module 124 may be better suited to the blood glucose monitoring to be conducted, at least initially – or in the second sub-range 318, indicating that the light spectroscopy blood glucose monitoring module 126 may be better suited to the blood glucose monitoring to be conducted, at least initially.

Thus it will be appreciated that Figure 1 illustrates a server apparatus 102 for monitoring blood glucose in a wearer 106 of a wearable device 104, the server apparatus 106 comprising a processor 110 and a memory 112, the server apparatus 102 being configured, under control of the processor 110, to execute instructions 114 stored in the memory 112: to perform a first mode of operation of blood glucose monitoring for the wearer 106 of the wearable device 104 using data obtained by a radio-frequency blood glucose monitoring module 124 in the wearable device 104. Server apparatus 102 is also configured to perform a second mode of operation of blood glucose monitoring for the wearer 106 of the wearable device 104 using data obtained by a light spectroscopy blood glucose monitoring module 126 in the wearable device 104. Server apparatus 102 may then perform a threshold comparison between a reference blood glucose value for the wearer 106 of the wearable device 104 and a threshold blood glucose value 314. Server apparatus 102 selects a first one of the first mode of operation and the second mode of operation

in dependence of the threshold comparison. A corresponding method is also described.

Thus, server apparatus 102 selects one of the modules 124, 126 as the initial module from which blood glucose measurement data will be taken for ongoing monitoring of blood glucose of the wearer 106.

For the sake of completeness, it is stated that, additionally or alternatively, the functionality described herein for server apparatus 102 may also be provided in the wearer's computing device 108.

After selection of a first one of the modules 124, 126, the wearer's blood glucose values may change to an extent that blood glucose measurement may more accurately be determined using the other of the modules 124, 126.

Turning back to the example of Figure 3(c), in this example, the initial selection by server apparatus 102 has been for the ongoing blood glucose monitoring to be determined based on the measurement data obtained by the radio-frequency blood glucose monitoring module 124. A measured value of blood glucose 320 – which may be a blood glucose value 320 determined by server apparatus 102 on the basis of the raw measurement data from the radio-frequency blood glucose monitoring module 124 – is illustrated in sub region 316 of the range 312 of overlap. In the situation whereby the wearer consumes food, for example a large meal having foodstuffs comprising a large sugar component, the raw measurement data obtained from the radio-frequency blood glucose monitoring module 124 indicates that the measured (determined) value 320 increases above the initial threshold value 314, as indicated by arrow 324. With such a determination, server apparatus 102 is configured to determine that, given the increase in the measured/determined value 320, more accurate monitoring may be conducted by the light spectroscopy blood glucose monitoring module 126.

In an alternative example, the initial selection by server apparatus 102 has been for the ongoing blood glucose monitoring to be determined based on the measurement data obtained by the light spectroscopy blood glucose monitoring module 126. A measured value of blood glucose 322 – which may be a blood glucose value 322 determined by server apparatus 102 on the basis of the raw measurement data from the light spectroscopy blood glucose monitoring module 126 – is illustrated in sub region 318 of the range 312 of overlap. In this situation whereby the blood glucose level 322 of the wearer drops below the initial threshold value 314, as indicated by arrow 326, server apparatus 102 is configured to determine that, given the decrease in the measured/determined value 322, more accurate monitoring may be conducted by the radio-frequency blood glucose monitoring module 124.

For one exemplary user, the range 312 of overlap may be across a range of 100 mg/dL, where both methods are acceptably linear.

Therefore, it will be appreciated that Figure 3 illustrates the radio-frequency blood glucose monitoring module 124 has a first range of operation 300 across a first range of blood glucose values 302, 304 and the light spectroscopy blood glucose monitoring module 126 has a second range of operation 306 across a second range of blood glucose values 308, 310, the first range 300 and the second range 306 having a range of overlap 312. The server apparatus 102 is configured for the threshold blood glucose value 314 to be in the range of overlap 312; and the server apparatus 102 is configured to determine when a measured value 320, 322 of blood glucose for the wearer 106 crosses the threshold 314 during blood glucose monitoring and, in dependence of the determination, to select a second one of the first mode of operation and the second mode of operation. In this context, “crosses” the threshold means when the determined blood glucose value 320, 324 goes from below the threshold to above it, or from above the threshold to below it.

In one arrangement, the initial selection between the first mode of operation and the second mode of operation to be performed without reference to the threshold blood glucose value. In this arrangement, the initial selection is performed by determining where, relative to the first and second ranges 300, 306, the received reference blood glucose value for the wearer is. Thus, in an alternative expression it will be appreciated that Figures 1 and 3 illustrate a server apparatus 102 for monitoring blood glucose in a wearer 106 of a wearable device 104, the server apparatus 102 comprising a processor 110 and a memory 112, the server apparatus 102 being configured, under control of the processor 110, to execute instructions 114 stored in the memory 112: to perform a first mode of operation of blood glucose monitoring for the wearer 106 of the wearable device 104 using data obtained by a radio-frequency blood glucose monitoring module 124 in the wearable device 104, the radio-frequency blood glucose monitoring module 124 having a first range of operation 300 across a first range of blood glucose values 302, 304; to perform a second mode of operation of blood glucose monitoring for the wearer 106 of the wearable device 104 using data obtained by a light spectroscopy blood glucose monitoring module 126 in the wearable device 104, the light spectroscopy blood glucose monitoring module 126 having a second range 306 of operation across a second range of blood glucose values 308, 310, the first range 300 and the second range 306 having a range of overlap 312; and to select one of the first mode of operation and the second mode of operation in dependence of a received reference blood glucose value for the wearer. A corresponding method is also described.

The Applicant has found that incorporation of a bio impedance reading into the determination of the measured/determined blood glucose value 320, 322 crosses the threshold 314. The bio impedance reading may be taken from any bio impedance sensor or from the bio impedance sensor module 128 in the wearable device 104, when one is provided. During operation of the wearable device 104 and the server apparatus 102, server apparatus 102 receives measurements from the bio impedance sensor module 128 which includes a component relating to the skin

resistance, capacitance and/or phase of the wearer, for example for a localised area of skin around the bio impedance sensor. Any changes in the skin resistance/capacitance/phase are indicative of a change in blood glucose for the wearer 106. For example for one individual, under similar environment settings will have a particular resistance X ohms for a certain blood glucose value Y mg/dL. When the Blood glucose value increases from Y to Y+deltaY, there is a corresponding change in the (local) skin resistance from X to, for instance, X+deltaX. From the measured reading from the bio impedance sensor module 128, the preferred mode of operation – which one of the radio-frequency or the light spectroscopy sensor modules 124, 126 to use data from – can be selected. For instance, a weight of either 0 or 1 is assigned to either the RF or the optical method. Other weighting values are contemplated, for example 0.7 for the RF method and 0.3 for the optical method. This technique may also be utilised with the example of Figure 3 where the threshold value is set at 300 mg/dL. Server apparatus 102 may be configured so that this threshold value is variable, to be set either by monitoring personnel or variable responsive to observations made data received during ongoing monitoring, for example, changes in the user's body make up, such as a change in (e.g. "local" body mass index, as may be measured with a BMI sensor in the apparatus 102). That is, server apparatus 102 is configured to vary the threshold blood glucose value.

Incorporation of the bio impedance sensor module into the wearable device offers the advantage that a preliminary determination of the glucose value can be made – using less complex processing – which is sufficiently accurate for server apparatus 102 to make a decision as to which of modules 124, 126 are to be used for ongoing monitoring.

Continuing with this example, if the blood glucose value received at the server apparatus 102 relating to the initial finger prick indicates that the wearer has a blood glucose value of 100 mg/dL, server apparatus 102 may assign weight 0 to the optical sensor module 126 and weight 1 to the RF sensor module 124 until the determined

blood glucose value reaches the threshold value, in this instance 300 mg/dL. Once the determined blood glucose value crosses the threshold – for example the determined value 320 crossing the threshold 314 as indicated by the arrow 324 in Figure 3(c) – the new (local) skin resistance is measured using the bio impedance sensor module 128 and a weight of 1 is assigned to the optical sensor module 126, and a weight of 0 is assigned to the RF sensor module 124. Thus, server apparatus 102 is configured to perform blood glucose monitoring by applying a weighting factor to at least one of determined first non-invasive measured blood glucose values and second non-invasive measured blood glucose values.

Therefore it will be appreciated that Figures 1 and 3 illustrate a server apparatus 102 configured to determine a bio impedance value for the wearer 106, the bio impedance value being obtained by data received from a bio impedance sensor 128; and to determine when a measured (determined) value 320, 322 of blood glucose for the wearer 106 crosses the threshold using the bio impedance value.

Ongoing monitoring of the determined value 320, 322 allows server apparatus 102 to track any alarm conditions of which the wearer may need to be aware. For example, if blood sugar becomes too low or too high (indicating a hypoglycaemic or a hyperglycaemic event), and alarm can be generated. It is useful to notify the wearer of the device of such an impending event so that the user may take preventive action, such as consuming medication and/or food in order to reduce the risk of the event occurring. The alarm can be generated in any one of a number of ways. For instance, server apparatus 102 can transmit information to the user's computing device for the alarm to be generated thereat. Additionally or alternatively, the wearable device 104 may be configured to emit an alarm such as an audible signal, or to generate a vibration action or similar.

The weighting factors may be applied by server apparatus 102 implementing the instructions 114 (software code) loaded into the memory 112 of the apparatus 102.

Additionally or alternatively, some form of hard-circuit switching may be effected to switch from one set of measurements to the other.

Figure 4 provides an alternative illustration of the system architecture. In this illustration, machine learning and weight assignment functions are optional. Some more detail referring to machine learning is given with respect to Figure 13 but, in summary, this can be used to determine optimal monitoring parameters for individual users based on the individual users' characteristics, and to set, for example, alarms for, say, hypoglycaemic and hyperglycaemic events accordingly. These results may be fine-tuned from additional data for the user, such as the user's heart rate, body temperature, pulse oximetry, sleep cycle, exercise activities and food intake, to name but a few.

Figure 5 provides a series of layout views of an exemplary wearable device 104. Figure 5(a) is an elevation view of the side of the wearable device intended to be worn against the user's skin, Figure 5(b) is a side view, and Figure 5(c) is an elevation view of the side of the wearable device intended to be worn away from the wearer's skin. The exemplary device of Figure 5 is comprised of a generally flat substrate 500 having a flexible section 502 about which fold lines may be made, the reasons for which will become apparent when reading Figure 6. Contact regions 506 are provided on either side of the flexible region 502, each of the contact regions having radio-frequency (patch) antennas 508 affixed thereto or mounted thereon, the antennas 508 forming part of the radio-frequency sensor module 124. Additionally or alternatively, other types of antennas may be used, for example slot antennas. In one example, the radio-frequency IC chip may be provided with an antenna on its substrate to radiate the radio-frequency signals. Light spectroscopy module 126, in this example, comprises a light source such as LED 510, photodiode 512 signal conditioning module 514. Wearable device 104 comprises first and second sets of bio impedance sensor electrodes, 516, 518, for positive and negative electrodes

respectively. An accelerometer 520 and/or a temperature sensor 521 may also be provided.

The PCB layer portions 522 are best viewed in Figure 5 (b), along with the RF IC 524 and the laminate fixture layers 526. A battery 528 is provided.

As viewed in Figure 5(c), a flexible cable 530 is used to join the section having the OLED display 532 to the sensor section.

Figures 1, 2 and 4 illustrate a wearable device 104 for blood glucose monitoring, the wearable device comprising: a radio-frequency blood glucose monitoring module 124 for obtaining a first non-invasive measured blood glucose measurement for a wearer 106 of the wearable device 104. A light spectroscopy blood glucose monitoring module 126 is provided for obtaining a second non-invasive measured blood glucose measurement for the wearer of the wearable device. A transmitter module 130 is provided for transmitting the first non-invasive measured blood glucose measurement and the second non-invasive blood glucose measurement to a second device, such as the user's computing device 108 and/or the server apparatus 102. A corresponding method is also described.

As mentioned above, the wearable device 104 may comprise a bio impedance monitoring module 128. This may be provided for obtaining a bio impedance measurement for the wearer 106 of the wearable device 104, and wherein the transmitter module 130 is configured to transmit the bio impedance measurement to the second device 102, 108.

Therefore, it will also be appreciated that Figure 1 illustrates a computing device 108 comprising a processor 132 and a memory 134, the computing device 108 being configured, under control of the processor 132, to execute instructions 136 stored in

the memory 134 to communicate information between the server apparatus 102 and the wearable device 104. A corresponding method is also described.

Figure 6 illustrates one way of wearing the wearable device 104 illustrated in Figure 5. In this respect, the device is worn on a part of the user's body, in this example the user's hand. Specifically, the device folds around the area in the user's hand between the thumb and the forefinger. The fold is around the fold lines 504 in the flexible section 502. As mentioned above, other types of wearable devices are contemplated. These may be worn on other parts of the body, such as the arm (or wrist) or on the ear, such as clipped to an ear lobe.

The bio impedance sensor may be configured to measure a "localised" bio impedance value for the localised area 602 around the area of the wearable device. In this respect, the extent and size of the localised area 602 depends on a number of factors including the wearer of the device, and the characteristics of the electronic components in the wearable device. For example, the localised area may be an area such as the area 602 illustrated in Figure 6 or another area, such as the wearer's arm below the elbow, or the whole arm.

Referring again to Figure 1, sensed signals obtained by radio-frequency blood glucose monitoring module 124 may be communicated to the server apparatus 102 via communications network 142. Server apparatus 102 is configured to process the received data to detect a change in blood glucose level for the wearer. For instance, server apparatus 102 may be configured to implement one or more algorithms using scattering parameter (S-parameter such as the S_{12} parameter) techniques in one or more of the time domain and also in the frequency domain. The raw data from the module 124 (and from module 126, for that matter) may be communicated using any suitable communications protocol, such as the TCP/IP protocols, LTE protocols, or, say, the short messaging service (SMS).

In one implementation the permittivity measurement is obtained using a CW/FMCW (radar) chip in the wearable device 104, for example in the radio-frequency blood glucose monitoring module 124. Additionally or alternatively, the variation in permittivity can be measured through the detection of phase difference between the input and output wave, and may provide a simple and low cost solution for this purpose.

Use of continuous wave modulation may be considered particularly beneficial when precise voltages have to be generated to control a voltage-controlled oscillator in a high-frequency integrated circuit chip used in the product. In such arrangements, the high-voltage may be generated by a stable ultralow noise digital to analog converter. When the digital to analog converter for the wearable device has to be ultralow power, and when the digital to analog converter requires an output buffer to provide for impedance to the voltage-controlled oscillator, other modulation protocols such as FMCW may require the digital to analog converter to operate at high-frequency (determined by the bandwidth of the FMCW chip and the duration of the sweep interval). Thus, a FMCW modulation scheme will cause higher power consumption and result in frequent charging/discharging of the battery, something which may be considered undesirable, particularly for a wearable device which may be intended for use over a prolonged period.

In one implementation, radio-frequency blood glucose monitoring module 124 senses a combined permittivity value for all different layers of skin as a single permittivity reference value. This is then correlated/calibrated to a known blood glucose value taken from a Blood glucose finger prick invasive test. Since the permittivity of the blood changes as the blood glucose concentration varies, this absolute permittivity for the combined skin changes in a similar fashion, which is detectable by dielectric spectroscopy, for example in the frequency domain. The determined blood glucose value may also be converted into the time domain as well.

A vector network analyser that measures S-parameters of materials may be employed to measure permittivity of a material, and/or other material properties. Permittivity (ε_r) can be extracted using, for example, the steps described in [12].

The Cole-Cole model for quantizing glucose dependent changes in electrical property can also be used.

$$\hat{\varepsilon}(\omega) = \varepsilon_c'(\omega) - j\varepsilon_c''(\omega) = \varepsilon_\infty + \sum_n \frac{\Delta\varepsilon_n}{1 + (j\omega\tau_n)^{(1-\alpha_n)}} + \frac{\sigma_i}{j\omega\varepsilon_0}$$

Where ω is the angular frequency, $\epsilon'_c(\omega)$ is the frequency dependent dielectric constant, $\epsilon''_c(\omega)$ is frequency dependent dielectric loss, n is the order of the Cole-Cole model, ϵ_∞ is high frequency permittivity, $\Delta\epsilon_n$ is the magnitude of the dispersion, $\tau_n$is the relaxation time constant, α_n is the parameter that allows for the broadening of the dispersion and σ_i is the static ionic conductivity. After determination of permittivity the correlation between blood glucose level and permittivity can be obtained from with 2-point calibration.

Figure 7 is a graph illustrating a series of curves of relative permittivity versus frequency for six exemplary types of body tissue [9]. In the exemplary graph, this shows how the permittivity of the layers 700 of dry skin, wet skin, muscle, blood, brain/white matter and fat vary with variations in the frequency of the applied radio-frequency wave. As will be seen, there is a region 702 of pronounced drop in permittivity. This region 702 corresponds with the range of operation 300 of the RF sensor module 124, as illustrated in Figure 3(a).So, while monitoring the data received from the RF sensor module 124, received as a series of signals from the wearable device 104, server apparatus 102 is able to detect a change in blood glucose from changes in the permittivity value.

Therefore, server apparatus 102 is configured to associate the data received from the radio-frequency blood glucose monitoring module as a series of combined values for plural tissue layers in the wearer's body, and to determine a change in blood glucose for the wearer from a determination of first and second combined values in the series of combined values being different from one another. Also, server apparatus 102 may be configured to associate the data received from the radio-frequency blood glucose monitoring module 124 as a series of combined permittivity values.

Traditionally radar is used to detect moving objects, and parameters such as the distance and speed. System 100 can be used to implement a novel way of using FMCW radar to measure one or more of absorption, delay, and phase of wave propagation in the blood which can be used to extract the amount of blood glucose. Other modulation schemes, including CW are contemplated.

Two exemplary methods for estimating the amount of blood glucose non-invasively are hereafter described.

ATTENUATION METHOD

The concept is articulated with the help of the equations described below.
As depicted in Figure 5(a) the flex board/cable 504when folded across the folding line will maintain a constant distance on either side of the fold. The wave propagating in the tissue can be represented as-

$$E(R) = E^{+}e^{-\gamma R} + E^{-}e^{\gamma R} \quad \text{--- Eq.1}$$

Where,

$$\gamma = \alpha + j\beta = j\omega\sqrt{\mu\varepsilon}\sqrt{1 - j\frac{\sigma}{\omega\varepsilon}}, \quad \text{---Eq2}$$

R= measuring site thickness

ε= Permittivity

σ= Conductivity

μ= permeability

μ and σ are approximately independent of glucose level and R is fixed for an individual. So the variation in ε will be represented in the measured attenuation. Measuring the amplitude of the wave can be done through FMCW, CW or another modulation scheme instead of an expensive vector network analyzer.

In addition, the variation in permittivity can be also measured through the phase difference between the input and output wave, by employing FMCW or other radar for this purpose.

$\tau = R/c_\varepsilon$ ---Eq.3

where c_ε is the velocity of wave in the medium.

Here τ is the time delay taken by the transmitted waveform to the target at distance R.

Note that R can also be determined for a particular person by using a device similar to a digital vernier calliper.

As the glucose monitoring sensor may have to be worn on a continuous basis, the first time a user uses the device, he (or she) may have to apply the sensor patch to the measurement site and the RF/mm-wave IC will generate signals such as FMCW. Since R is fixed for one user and τ can be found out from the FFT (Fast Fourier Transform) signal processing in the baseband, the value of c_ε which is medium-dependent may be taken as the first reference point for calibration of subsequent sensor signals. This value of c_ε may be stored in the microcontroller or software on the phone (and/or at server level) along with the Blood Glucose finger prick value to

serve as the calibrated reference point for further non-invasive sensor readings.

Phase information may be extracted from this time delay τ. There is a phase shift observed during experimentation when blood glucose rises.

(2) PHASE INFORMATION

Figure 8 illustrates a radar sweep for a RF module implementing FMCW, the second exemplary method. f_0 is the starting frequency; f_1 is the end frequency of the linear increasing sweep; B is the bandwidth which is difference between f_1 and f_0; T is the sweep period.

$\tau=2R/c_\varepsilon$ ---Eq.4

Here τ is the time delay taken by the transmitted waveform to the target at distance R and to return.

c_ε is the velocity of light in the medium. In this example, the medium is biological skin or the interested measurement site.

The beat frequency (f_B) is given by equation 5

$f_B=f_T-f_R= \alpha * \tau = (2R*B)/(c_\varepsilon*T)$ ------Eq. 5

The rate of change of frequency= $\alpha=B/T$ -----Eq.6

Since α, f_T are known beforehand, R is fixed for a user and f_B can be found from the baseband signal, so it is simple to calculate the value of c_ε from equation 7.

$c_\varepsilon \propto 1/\sqrt{\varepsilon}$ ---- Eq. 7

A simplified effective permittivity (ε_{eff}) can be calculated as-

$$\varepsilon_{eff} = \frac{t_1 + t_2 + t_3 + \ldots}{\left(\frac{t_1}{\varepsilon_1} + \frac{t_2}{\varepsilon_2} + \frac{t_3}{\varepsilon_3} + \ldots\right)} \quad \text{-----Eq. 8}$$

Where $t_{1, 2, \ldots n}$= thickness of individual skin layers

$\varepsilon_{1, 2, \ldots n}$= permittivity of individual skin layers

As shown in Eq. 7, the velocity of light is dependent on the permittivity of the medium. The current approach may use combined permittivity values (ε_{eff}) for all different layers of skin as one single permittivity reference value which is correlated to the Blood glucose finger prick value. Since, the permittivity of the blood changes as the blood glucose concentration increases, this absolute permittivity for the combined skin increases in a similar fashion, hence the time delay τ also increases and the c_ε decreases, increasing the beat frequency f_B.

A fast Fourier transform can be performed on the beat frequency to reveal the amplitude and/or frequency shift information.

Sensed signals obtained by light spectroscopy blood glucose monitoring module 126 may also be communicated to the server apparatus 102 via communications network 142. Server apparatus 102 is configured to process the received data to detect a change in blood glucose level for the wearer. For instance, server apparatus 102 may be configured to implement one or more algorithms to that end.

Near infrared light is an attractive method as it can deeply penetrate into the tissue to determine the amount of blood glucose [6]. The amount of light scattered decreases with an increase in the amount of blood glucose content. Hence, a photodiode and light source can be used to estimate the amount of blood glucose. However, previous experiments conducted by one of the inventors in the current application [7] suggest that the variation of tissue thickness, for example, ear lobe

thickness (which can be used as a measurement site) and skin tone can contribute to the degradation of the correlation coefficient of near infrared light, and mid infrared light with respect to the amount of blood glucose. The degradation of the correlation coefficient makes this method less suitable if it is used as the only method to determine blood glucose for multiple individuals without calibration.

Figure 9 (and Figure 10, which implements symbols in place of the dashed lines of Figure 9) is a graph illustrating a series of blood glucose measurement values implementing the current non-invasive techniques compared with invasive techniques. The continuous predicted blood glucose is given with respect to reference blood glucose of a healthy human volunteer using the radio-frequency method. This experiment was conducted for an 87-minute duration during which sugar drink and chocolate cookies were consumed 18 minutes apart. Distinct sensor peaks can be observed in the 45^{th} and 62^{nd} minutes of the experiment (indicated by the solid line). Blood Pricks using a One Touch Ultra (TM) device were taken every 5-7 minutes to verify the surge in blood glucose near the sensor peaks (indicated by the chain line). Rate limiting filtering was applied to the raw sensor data, indicated by the dashed line. The sensor yields non-Invasive data every 60 seconds. It has been found that data, when plotted on the Clarke error grid, can satisfy the ISO15197 standard.

Figure 11 is a Clarke Error Grid of the results from Figure 10.

Figure 12 shows the results from comparing the non-invasive near infrared (NIR) light spectroscopy with respect to blood glucose results for an individual as well as multiple individuals. Figure 12 (a) shows the potential of a NI-CGMS system using the NIR approach described herein, where the data is taken along with an invasive blood glucose test two times for 4 days in an uncontrolled and non-calibrated environment. Figure 12 (b) data is taken for 24 random individuals using NIR (980nm), Near IR (1200, 1450, 1550nm) and the predicted glucose concentration is

plotted with respect to reference blood glucose. A total of 96 sample points indicate readings in Clarke grids A (73.34%) and B (26.66%) 1200 which is clinically acceptable. The 24 individuals are divided into 2 groups comprising of 13 and 11 individuals with similar skin tone (visually filtered), but no age restriction. The slope intercept equation 1202 may be used to plot predicted glucose reading for Figure 12 (b), whereas for Figure 12 (a) the correlation coefficient may be found out between the sensor and BG values to perform Clarke error grid analysis.

Figure 12(a) shows non-invasive result of blood glucose value vs. NIR light source for an Individual with type 1 diabetes, and Figure 12(b) shows the result of blood glucose value vs. NIR light source for multiple Individuals with or without diabetes.

Thus, it will be appreciated that server apparatus 102 is configured to compare the measured blood glucose value with historical blood glucose data and, from the comparison, to determine a change in blood glucose for the wearer. Historical blood data may comprise data obtained from the wearer, whether from module 124 or from module 126, or of data obtained from a group of sample subjects (each of whom may or may not have diabetes). The apparatus 102 is configured to compare the measured blood glucose value with a slope-intercept equation from the historical data of the non-invasive sensor(s). (In this context, “measured blood glucose value” may refer to the raw data obtained by the sensor(s) in the modules 124, 126, or this raw data, after it has been processed by server apparatus 102.

The above mentioned earlier experiments [7] suggest that the variation of tissue thickness, for example, earlobe thickness which can be used as a measurement site and skin tone can contribute to the degradation of correlation coefficient of near infrared light with respect to the amount of blood glucose. The degradation of correlation coefficient during a hypoglycaemic condition makes this method less suitable if used as the only method to determine blood glucose. An important insight

after the experiments was that the non-invasive algorithm may be unique to every individual.

As mentioned above, a machine learning algorithm may be used to monitor or track the data obtained by the sensors 124, 126 in the wearable device 104. The tracked data may be used to refine/fine-tune system data, such as the thresholds at which the switching between RF sensor data and optical sensor data, and/or the thresholds at which alarms may be generated.

A complete non-invasive continuous glucose monitoring system solution may not only lie in the above-described hardware, but also in a machine learning algorithm which may be implemented in, for example, an android/iOS application, in one or more servers (for example one or more cloud servers), in an embedded real-time operating system in a fixed or mobile device, or at least a component of the algorithm being implemented therein. Unsupervised learning and reinforcement learning approaches can be one set of methods that can be applied to dynamically update the weights assigned to the two non-invasive methods to determine blood glucose.

As mentioned above, bio impedance may be measured locally (ear lobe, arm, nostril, leg etc.) to see the changes in terms of capacitance, resistance, phase to suggest automatic changes in calibration requirement. Upon detection of a change in the bio impedance reading (which will take few weeks depending on the person's lifestyle), server apparatus 102 may be configured so that the algorithm will define a new calibration reference point i.e. a new capacitance value and new light spectroscopy reference sensor value which will serve as reference calibration point for subsequent non-invasive sensor readings. Since multiple calibrations may be required daily for all current CGMS devices, it is proposed to adopt initially two calibrations per day. This may serve as a two-point reference calibration scheme for continuous blood glucose monitoring throughout the day.

The facility to define a new calibration reference point be beneficial because, over the course of several weeks, the user's fat content at the site of sensor measurement may change, thus requiring re-calibration by use of blood prick sensor readings. Alternatively, since the bio impedance of the local area is measured, the amount of fat change can be detected. If this is significant, a new reference point from the previous user data in the server can be used to calibrate new incoming radio-frequency data such that the historical data of a user remains valid. Thus, the server apparatus is configured to calibrate (or re-calibrate) historical data relating to the wearer based on a change in the bioimpedance value.

With the help of machine learning/deep learning algorithms, optionally along with an android/iOS app to track users daily motion activities (like a pedometer) with an accelerometer, and bio-impedance, heart rate, pulse oximetry sensor build in the sensor patch/fitness band to dynamically change and predict the weight assigned to the two methods independently providing non-invasive glucose results. Figure 13 shows an exemplary correlation coefficient and weight assignment scheme to enhance the total correlation of multi-sensor method, in order to predict blood glucose content which is clinically acceptable.

Bio-impedance along with pulse oximetry and/or heart rate can be used to precisely determine and predict impending hypoglycaemic events during sleeping. During a hypoglycaemic event, the user's heart rate is expected to rise, as the user mounts an autonomic causing tachycardia. However, some patients may not exhibit a rise in heart rate with hypoglycaemia if they have a problem in the autonomic nervous system.

Machine learning uses inputs/features/trends from wearer's heart rate, exercise patterns, sleep cycles (including duration), temperature (core/skin) as optional parameters which, when used, help to enhance the accuracy of the switching

threshold for bio impedance. These optional parameters are unique for every individual and hence the weight assignment for the neural network layers vary, and linear regression /non-linear regression techniques can be used depending on the input data (or training data) to the machine learning system.

Implementation of neural networks/machine learning techniques on the gathered user data may be effected. Upon gathering sufficient data, the machine is trained using this data and the subsequent sensor data does not require calibration from the user (in terms of the SMBG finger pricks).

The weights assigned to neural network layers may not be similar for all individuals. Data trends from heart rate, exercise, sleep patterns, local bio impedance, and pulse oximetry can be used:

1) Heart rate - both resting and passive - throughout the day,
2) exercise (measured using, for example, a pedometer or similar device),
3) sleep patterns (light, deep, REM),
4) local bio impedance (tracking the changes in tissue fat, water content - by measuring Resistance, Capacitance, Phase).

Machine learning may work on the following principle. Features from the RF wave signals may be analysed in the time and frequency domain. Features in the time domain (mean, median, variance, standard deviation, time delay) are computed. Features in the frequency domain being used include signal power, magnitude, total spectrum power, noise power spectrum, normalized power (normalized power of the spectrum may be computed in intervals for example every 10 minutes, with the frequency of the CGM in this example being 10 minutes), and frequency shift.

The capacitance of the different skin/tissue layers – fat, wet skin, dry skin, blood, bone for example – may be taken as one unified capacitance which serves as the reference for the combined permittivity. Changes in the permittivity of the red blood

cell count due to changes in blood glucose can be measured using, for example, one of the RF wave techniques described above. As a number of the layers – the bone, fat, wet skin, dry skin and permittivity – do not change in the short-term, but only extended periods, the CGM utilising RF wave for prediction of blood glucose is feasible for implementing in a non-controlled environment.

As shown in Figure 13, the correlation coefficients a_j to e_j of various methods proposed (light spectroscopy, dielectric spectroscopy, temperature, BMI, pulse oximetry) may be included inside a machine learning algorithm for it to adapt to a dynamic measurement environment. This reduces the amount of calibration required by the CGMS from an average twice per day to once per day after an estimated first month of using the proposed NI-CGMS technique(s). After sufficient user data have been obtained, using both invasive and non-invasive techniques, a zero calibration scheme may be realised. Deep learning algorithms along with the proposed multi-sensor approach can be implemented to achieve this zero calibration scheme.

In one example implementation scenario, upon the first usage of the system, the user is instructed to calibrate upon system start indicated as point 1 in the calibration block. This is done to calculate the minimum and maximum thresholds for individual sensors. Next, the user wears the sensor patch and the second point of calibration is taken (preferably before consuming food). Point 3 of the calibration is taken 20-30 minutes after consuming food. This is done to get the direction of phase shift (or the parameters we are measuring example delay, frequency domain analysis) and record changes in the sensor parameters. Note calibration points 1 to 3 may need to be done only once during the sensor lifetime.

Calibration points 4and 5 are to be done daily approximately after every 12 hours. It is predicted that upon continuously using the NI-CGMS device, the calibration can be reduced to once per day. Eventually after sufficient data points of both invasive and

non-invasive methods are available in our system, zero calibration can be achieved with the help of deep learning and multi-sensor data.

Server 102 may implement a bio-impedance measurement component to compute user parameters such as respiration rate, fat percentage and water content and sleep cycle/stage. Pulse oximetry may be used to calculate oxygenated deoxygenated blood counts, and pulse rate/heart rate. Temperature reading comprising of ambient and skin surface may be taken. Sensed bio-impedance, pulse oximetry, and temperature data can serve as correction factors for the two methods - light spectroscopy and dielectric spectroscopy to compute blood glucose content.

After attaining individual coefficients (a_j to e_j) for the calibration models, dynamic variation of factors/parameter such as bio-impedance, temperature, pulse oximetry, heart rate, amount of exercise, food intake in addition to processing of data obtained by the light spectroscopy and dielectric spectroscopy methods (RF/mmwave/terahertz) in combination with machine learning and deep learning algorithms may be used to assign respective weights for the data obtained using the light spectroscopy and dielectric spectroscopy methods.

The approximate regions of high and low blood glucose can be precisely determined with the help of multi-sensors for example, bio-impedance, pulse oximetry, heart rate and temperature sensors. For this discussion, the sensors shown in the Figure 13 are shown as having a multiplicity of detection parameters. Various implementations of devices and/or systems, as described herein, may include fewer sensor components or detection parameters and remain within the scope of the disclosure. Alternately, other implementations of devices and/or systems may include additional components, sensors, or various combinations of the described components, sensors, and remain within the scope of the disclosure.

The main algorithm combining machine learning, deep learning, multi-sensor data is used to predict blood glucose results and provide hypo/hyperglycaemic alerts.

The proposed system with the usage of multiple parallel sensors (dielectric spectroscopy, light spectroscopy and local bio impedance sensors) and additional parameters (local BMI, skin thickness, heart rate, pulse oximetry, temperature(core, skin), movement tracker, food intake, for example) maximizes the signal to noise ratio and sensitivity required for clinical acceptance. For instance, a highly integrated multiple sensor patch can be placed onto a skin fold with no irritation. A wearable device akin to a pedometer can be used. An optional heart rate sensor to increase sensitivity in detecting hypoglycaemia without a lag time may be integrated into the multi-sensor approach. The collected non-invasive CGMS data is evaluated for alerting impending hypoglycaemic and hyperglycaemic events based on multiple parameters. Using the described techniques, clinical precision may be attained.

For this foregoing discussion, the devices and systems illustrated in the figures are shown as having a multiplicity of components. Various implementations of devices and/or systems, as described herein, may include fewer components and remain within the scope of the disclosure. Alternately, other implementations of devices and/or systems may include additional components, or various combinations of the described components, and remain within the scope of the disclosure. The wearable device can be worn on any part of body as long as it fits to the shape, for example, earlobe, nostril, arm and fingertip.

According to [11] “For instance, at 10 kHz the impedance modulus of the 300 mg/dl sample in the first animal was 74.0 Ω, while in the second animal it was 71.3 Ω. This suggests that possible clinical applications of the impedance spectroscopy approach would require calibration over each subject.”

We cater for this change in from person to person through customised algorithm catered for an individual through machine learning implemented using neural networks which may utilise linear regression and non-linear regression techniques. Switching between RF and light spectroscopy methods takes place with the help of Resistance, capacitance phase parameters from the local bio-impedance sensor

As may have been realised from the foregoing discussion, implementation of the techniques disclosed herein may allow realisation of significant technical benefits.

For instance, a true non-invasive solution implementing multiple sensors may obviate the requirement hitherto prevalent in the field of requiring invasive monitoring. Known CGMS systems typically have a limited life cycle of between three and seven days. Wearable devices implementing the techniques described herein may have lifetimes of between around 12 and 18 months, depending on the precise CMOS IC lifetime. Use of a CMOS, along with the described light source and sensing components may lead to a greatly-enhanced product life.

A number of known CGMS systems require a significant sensor warm up time of between around 2 and 10 hours. Wearable devices implementing the techniques described herein may not require any warm up time.

A number of known CGMS sensors are prone to bio-fouling. The disclosed NI-CGMS device is not prone to bio-fouling as it is non-invasive

Many existing CGMS devices are extremely costly. It is projected that the wearable device described above will be an extremely low cost and low power solution.

Many known non-Invasive techniques are not accurate enough to meet clinical standards. With the proposed wearable sensor, two independent methods to

determine glucose concentration will enhance the accuracy of individual methods when combined to meet clinical requirements.

Varying skin tone and skin thickness for multiple individuals using the same non-invasive device requires tedious and multiple calibration cycles with blood glucose meter device.

Use of the above radio frequency module (e.g. utilising mm wave technology) does not depend on skin tone and skin thickness is taken into account in the algorithm, hence simple calibration as shown in Figure 13 can be achieved.

For the proposed light spectroscopy method, a suitable calibration reference point may be chosen automatically when the user uses the NI-CGMS device. The machine learning algorithm can automatically sense variations in the accuracy of the light spectroscopy sensor's output and pick a new calibration point in the event that the skin parameters have changed.

Some know CGMS systems have reduced sensitivity in determining true hypoglycaemic events. The described light spectroscopy and dielectric spectroscopy techniques, with the help of bio-impedance, heart rate, temperature, and accelerometer measurements can precisely predict/detect hypoglycaemic events.

Some known CGMS sensors have a lag time of between around 5-15 minutes to report blood glucose concentration since these sensors measure interstitial fluids (ISF) glucose concentration and require three or more stage digital filtering. The techniques described herein may allow real time or near real time continuous glucose measurement with minimum lag, which may be at most of the order of a few seconds to one minute because of sensor signal post processing since blood glucose is measured non-invasively. The above-described wearable device does not require

multi stage filtering; the device is not limited to dealing with Nano ampere sensor currents as compared to some known CGMS sensors.

Some known CGMS sensors have major portability issues. A separate wireless transceiver may be required to be attached to the body (e.g. in the abdomen area) which is connected to in-vivo enzymatic sensors. For an ex-vivo micro dialysis method, a separate tube carrying ISF fluid needs to be attached to the waist/abdomen area and connected to external sensor for glucose readings. Instead, the inventors propose a wearable thin, small area, waterproof sensor as described above, with the attendant sensing and detecting techniques, which can be connected to a smart watch or similar communicating device.

Known non-invasive devices suffer from degradation of signal to noise ratio and sensitivity. In the current techniques, the signal-to-noise ratio can be increased by using methods that employs parallel monitoring using multiple methods and parameters. Our system uses a multi-sensor approach and employs various parallel methods to maximize the signal to noise ratio.

The techniques described herein may allow a NI-CGMS to wirelessly link with artificial pancreas for automatic insulin injection.

The techniques use, for example, FMCW for dielectric spectroscopy and detecting blood glucose concentration. Other modulation schemes, frequency bands could be used, such as CW, AM and PM.

The techniques may use frequency bands from 1- 300Ghz.

Use of machine learning techniques may bring about a system in which zero calibration is required.

It will be appreciated that the invention has been described by way of example only and that various modifications may be made to the techniques described above without departing from the spirit and scope of the invention.

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CLAIMS

1. Server apparatus for monitoring blood glucose in a wearer of a wearable device, the server apparatus comprising a processor and a memory, the server apparatus being configured, under control of the processor, to execute instructions stored in the memory:

to perform a first mode of operation of blood glucose monitoring for the wearer of the wearable device using data obtained by a radio-frequency blood glucose monitoring module in the wearable device;

to perform a second mode of operation of blood glucose monitoring for the wearer of the wearable device using data obtained by a light spectroscopy blood glucose monitoring module in the wearable device;

to perform a threshold comparison between a reference blood glucose value for the wearer of the wearable device and a threshold blood glucose value; and

to select a first one of the first mode of operation and the second mode of operation in dependence of the threshold comparison.

2. The server apparatus of claim 1, wherein:

the radio-frequency blood glucose monitoring module has a first range of operation across a first range of blood glucose values;

the light spectroscopy blood glucose monitoring module has a second range of operation across a second range of blood glucose values, the first range and the second range having a range of overlap;

wherein the server apparatus is configured for the threshold blood glucose value to be in the range of overlap; and

wherein the server apparatus is configured to determine when a measured value of blood glucose for the wearer crosses the threshold during blood glucose monitoring and, in dependence of the determination, to select a second one of the first mode of operation and the second mode of operation.

3. The server apparatus of claim 1 or claim 2, configured:

to determine a bio impedance value for the wearer, the bio impedance value being obtained by data received from a bio impedance sensor; and

to determine when a measured value of blood glucose for the wearer crosses the threshold using the bio impedance value.

4. The server apparatus of claim 3, wherein the bio impedance value is a local bio impedance value for a localised region of the wearer's body, the local bio impedance value being obtained by a bio impedance sensor module in the wearable device.

5. The server apparatus of claim 4, configured to calibrate historical data relating to the wearer based on a change in the bio impedance value.

6. The server apparatus of any preceding claim, configured to vary the threshold blood glucose value.

7. The server apparatus of claim 6, configured to vary the threshold blood glucose value in dependence of measured blood glucose values for the wearer determined over a period of time.

8. The server apparatus of any preceding claim, configured to associate the data received from the radio-frequency blood glucose monitoring module as a series of combined values for plural tissue layers in the wearer's body, and to determine a change in blood glucose for the wearer from a determination of first and second combined values in the series of combined values being different from one another.

9. The server apparatus of claim 8, configured to associate the data received from the radio-frequency blood glucose monitoring module as a series of combined permittivity values.

10. The server apparatus of any of claims 2 to 9, configured to compare the measured blood glucose value with historical blood glucose data and, from the comparison, to determine a change in blood glucose for the wearer.

11. The server apparatus of claim 10, wherein the historical blood glucose data comprises data obtained from the wearer, or data obtained from a group of sample subjects.

12. The server apparatus of claim 11, configured to compare the measured blood glucose value with a slope-intercept equation from the historical data.

13. The server apparatus of any preceding claim, configured to perform blood glucose monitoring by applying a weighting factor to at least one of determined first non-invasive measured blood glucose values and second non-invasive measured blood glucose values.

14. The server apparatus of any preceding claim configured to receive an initial reference blood glucose value from a transmitting device in or associated with a political cause meter.

15. Server apparatus for monitoring blood glucose in a wearer of a wearable device, the server apparatus comprising a processor and a memory, the server apparatus being configured, under control of the processor, to execute instructions stored in the memory:

to perform a first mode of operation of blood glucose monitoring for the wearer of the wearable device using data obtained by a radio-frequency blood glucose monitoring module in the wearable device, the radio-frequency blood glucose monitoring module having a first range of operation across a first range of blood glucose values;

to perform a second mode of operation of blood glucose monitoring for the wearer of the wearable device using data obtained by a light spectroscopy blood glucose monitoring module in the wearable device, the light spectroscopy blood glucose monitoring module having a second range of operation across a second range of blood glucose values, the first range and the second range having a range of overlap; and

to select one of the first mode of operation and the second mode of operation in dependence of a received reference blood glucose value for the wearer.

16. A wearable device for blood glucose monitoring, the wearable device comprising:

a radio-frequency blood glucose monitoring module for obtaining a first non-invasive measured blood glucose measurement for a wearer of the wearable device;

a light spectroscopy blood glucose monitoring module for obtaining a second non-invasive measured blood glucose measurement for the wearer of the wearable device; and

a transmitter module for transmitting the first non-invasive measured blood glucose measurement and the second non-invasive blood glucose measurement to a second device.

17. The wearable device of claim 16, further comprising a bio impedance monitoring module for obtaining a bio impedance measurement for the wearer of the wearable device, and wherein the transmitter module is configured to transmit the bio impedance measurement to the second device.

18. The wearable device of claim 16 or claim 17, wherein the radio-frequency blood glucose monitoring module is configured for operation in a frequency band of between around 24 GHz to 24.25 GHz.

19. A computing device comprising a processor and a memory, the computing device being configured, under control of the processor, to execute instructions stored in the memory to communicate information between the server apparatus of any of claims 1 to 15 and the wearable device of any of claims 16 to 18.

20. A method for monitoring blood glucose in a wearer of a wearable device, the method being implemented in the server apparatus of any of claims 1 to 15.

21. A method for obtaining non-invasive measured blood glucose measurements, the method being implemented in the wearable device of any of claims 16 to 18.

22. A method of communicating information between the server apparatus of any of claims 1 to 15 and the wearable device of any of claims 16 to 18, the method being implemented in the computing device of claim 19.

23. A computer program product comprising instructions for a server apparatus to implement the method of claim 20.

24. A computer program product comprising instructions for a computing device to implement the method of claim 22.

25. A computer program comprising instructions for a server apparatus to implement the method of claim 20.

26. A computer program comprising instructions for a computing device to implement the method of claim 22.

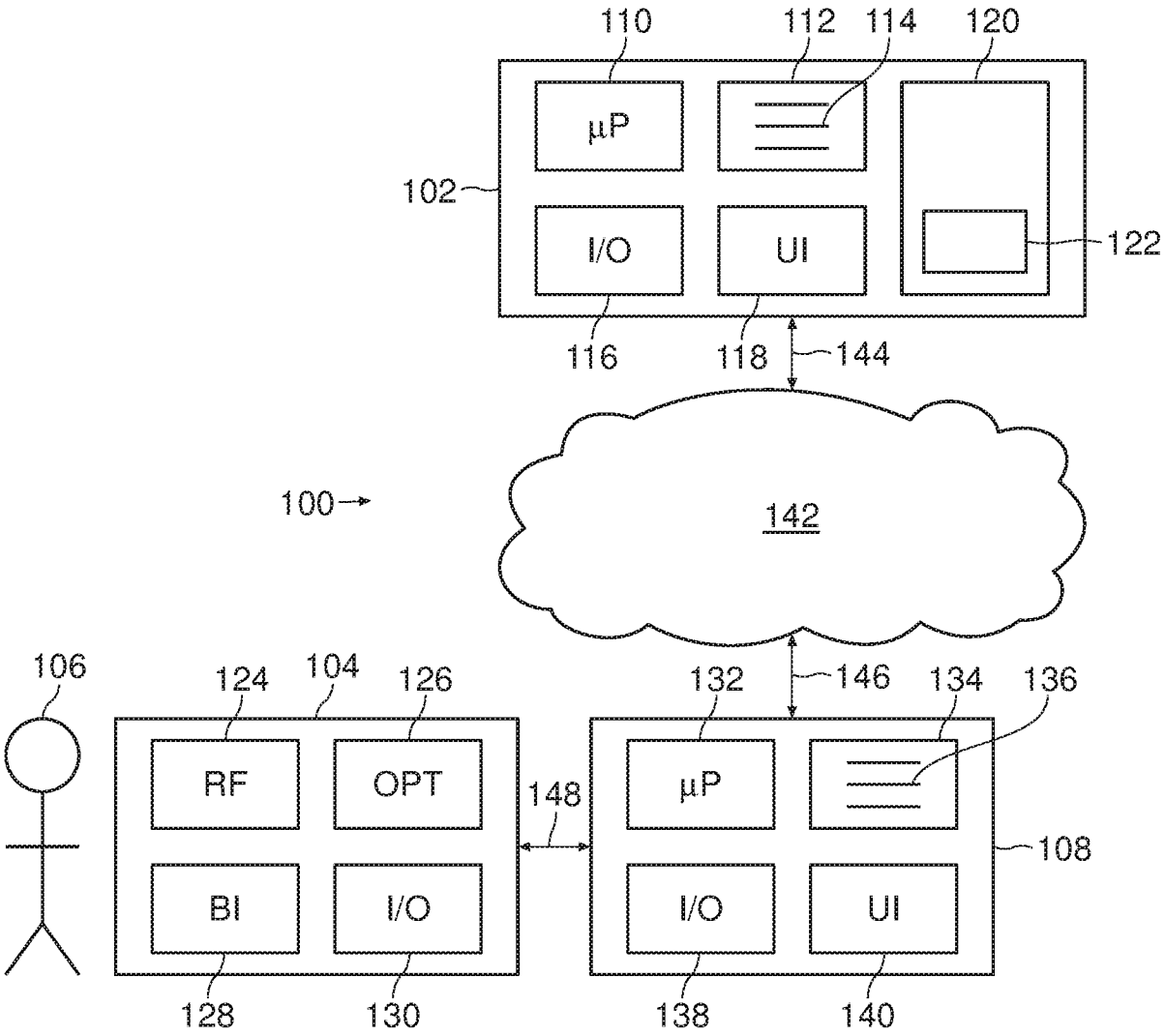
110
112
114
120
µP
102
I/O
UI
122
116
118
144
100
142
106
124
104
126
132
146
134
136
RF
OPT
148
µP
108
BI
I/O
I/O
UI
128
130
138
140

FIG. 1

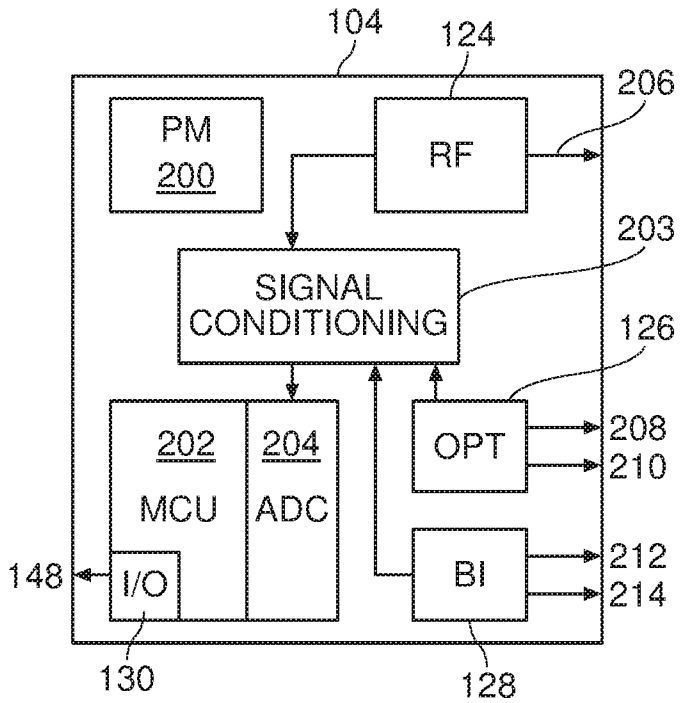
104
124
206
PM
200
RF
203
SIGNAL
CONDITIONING
126
202
MCU
204
ADC
OPT
208
210
148
I/O
BI
212
214
130
128

FIG. 2

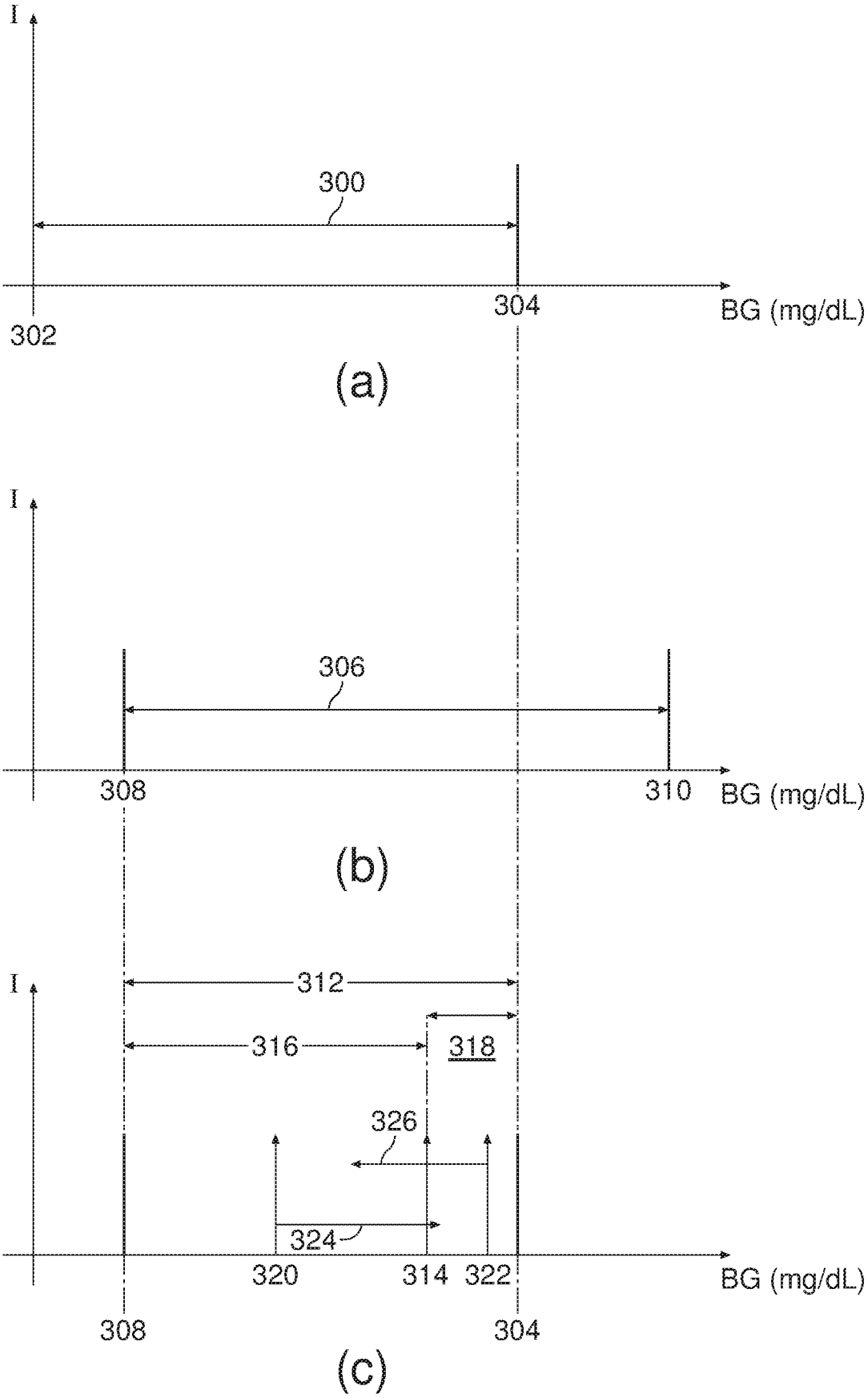
I
300
302
304
BG (mg/dL)
(a)
I
306
308
310
BG (mg/dL)
(b)
I
312
316
318
326
324
320
314
322
BG (mg/dL)
308
304
(c)

FIG. 3

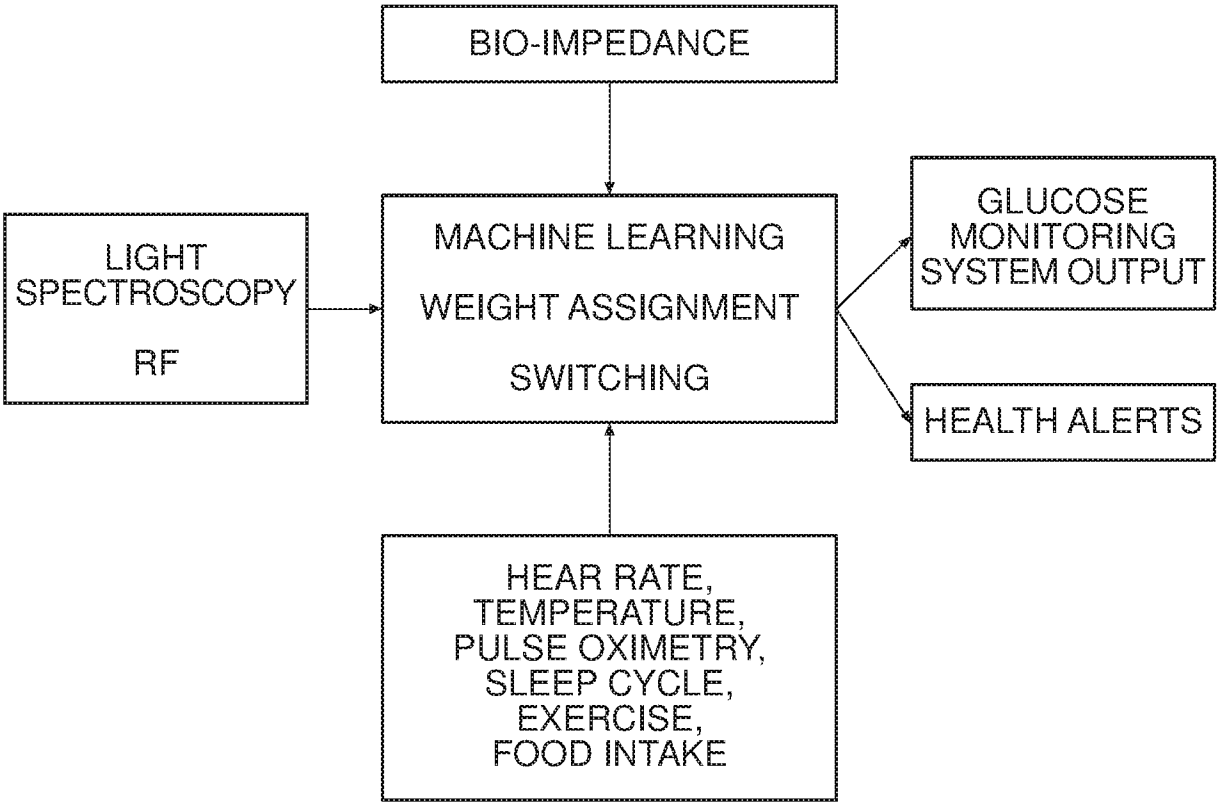
BIO-IMPEDANCE
LIGHT SPECTROSCOPY
RF
MACHINE LEARNING
WEIGHT ASSIGNMENT
SWITCHING
GLUCOSE MONITORING SYSTEM OUTPUT
HEALTH ALERTS
HEAR RATE, TEMPERATURE, PULSE OXIMETRY, SLEEP CYCLE, EXERCISE, FOOD INTAKE

FIG. 4

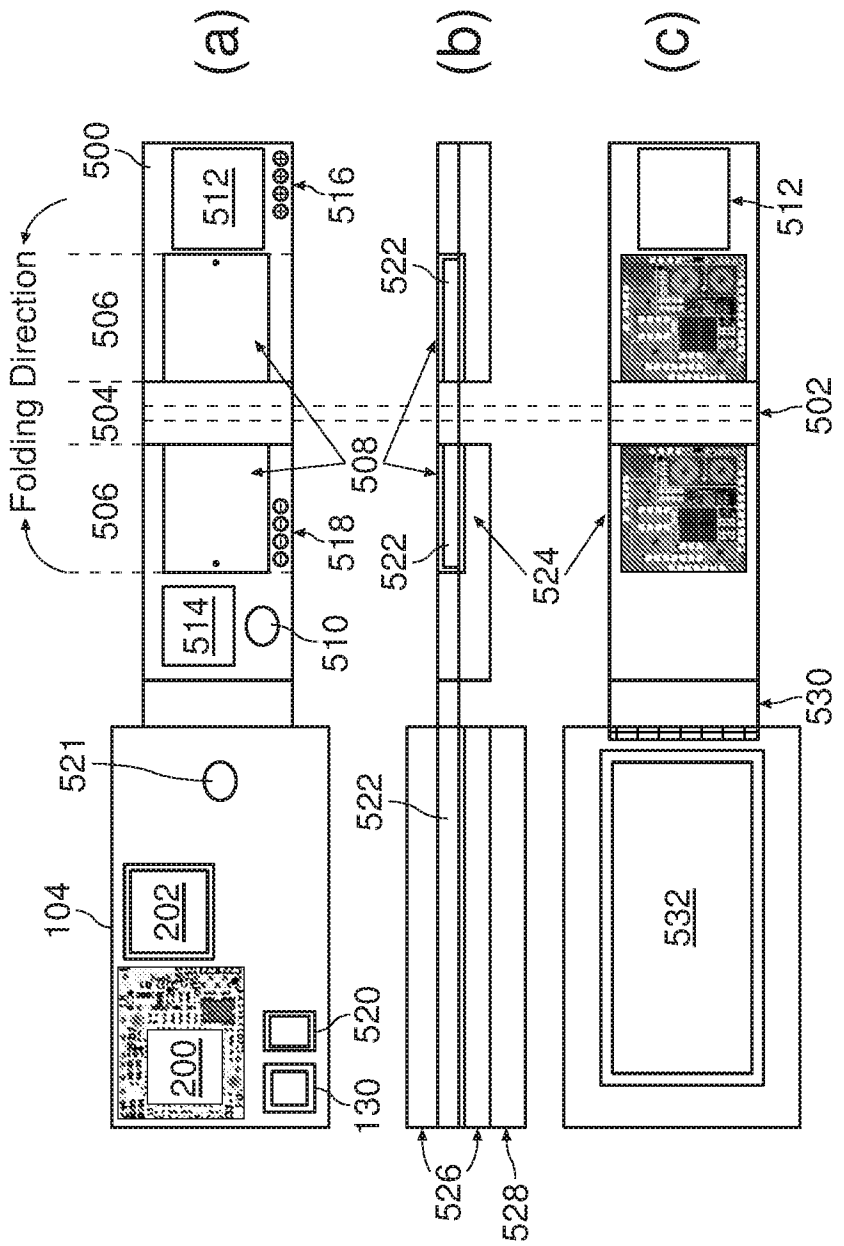
(a)
(b)
(c)
Folding Direction
500
506
504
506
512
516
514
510
518
508
522
524
502
530
521
522
104
202
200
520
130
526
528
532

FIG. 5

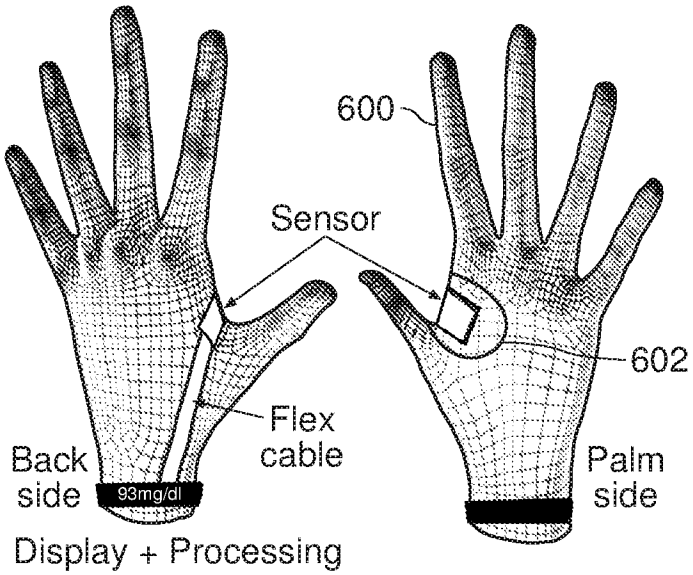
600
Sensor
602
Flex
cable
Back
side
93mg/dl
Palm
side
Display + Processing

FIG. 6

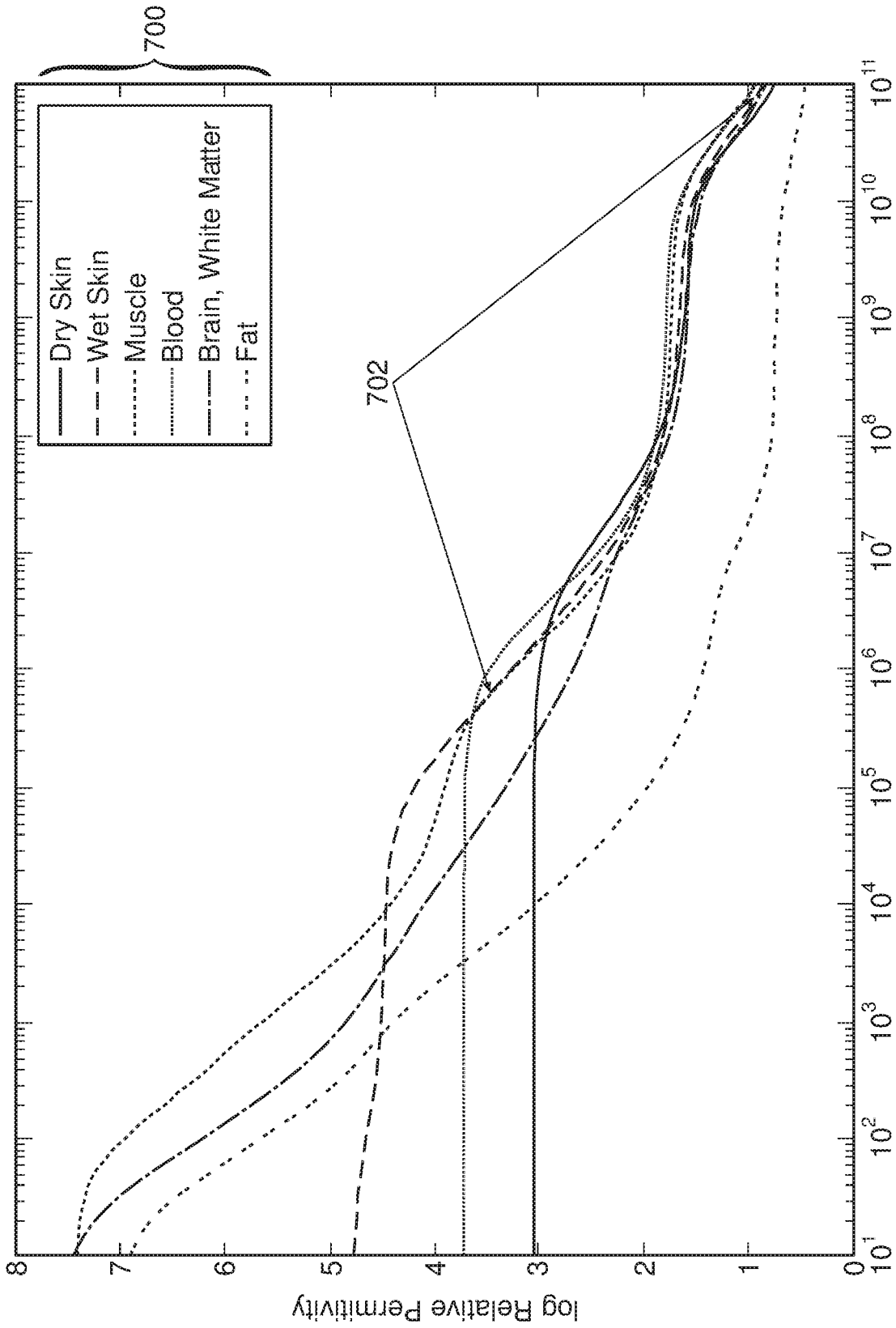
700
Dry Skin
Wet Skin
Muscle
Blood
Brain, White Matter
Fat
702
log Relative Permitivity
Frequency (Hz)
8
7
6
5
4
3
2
1
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
10^8
10^9
10^{10}
10^{11}

FIG. 7

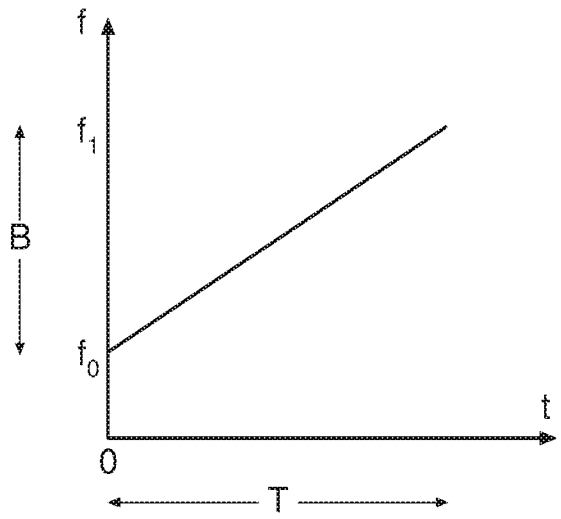

FIG. 8

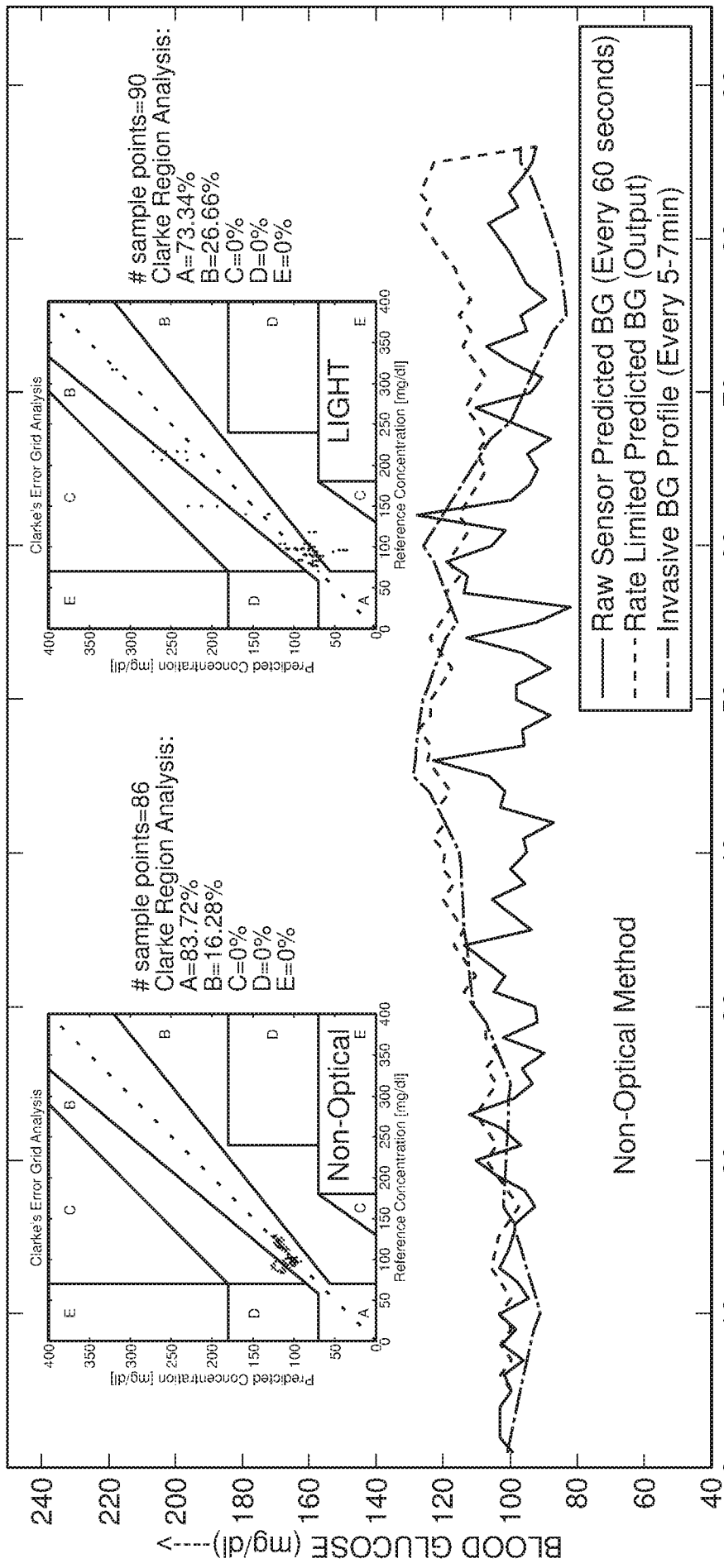
BLOOD GLUCOSE (mg/dl)----->
TIME (MINUTES)----->
Raw Sensor Predicted BG (Every 60 seconds)
Rate Limited Predicted BG (Output)
Invasive BG Profile (Every 5-7min)
Non-Optical Method
SUGAR DRINK
CHOCOLATE COOKIES
Clarke's Error Grid Analysis
Predicted Concentration [mg/dl]
Reference Concentration [mg/dl]
Non-Optical
sample points=86
Clarke Region Analysis:
A=83.72%
B=16.28%
C=0%
D=0%
E=0%
LIGHT
sample points=90
Clarke Region Analysis:
A=73.34%
B=26.66%
C=0%
D=0%
E=0%

FIG. 9

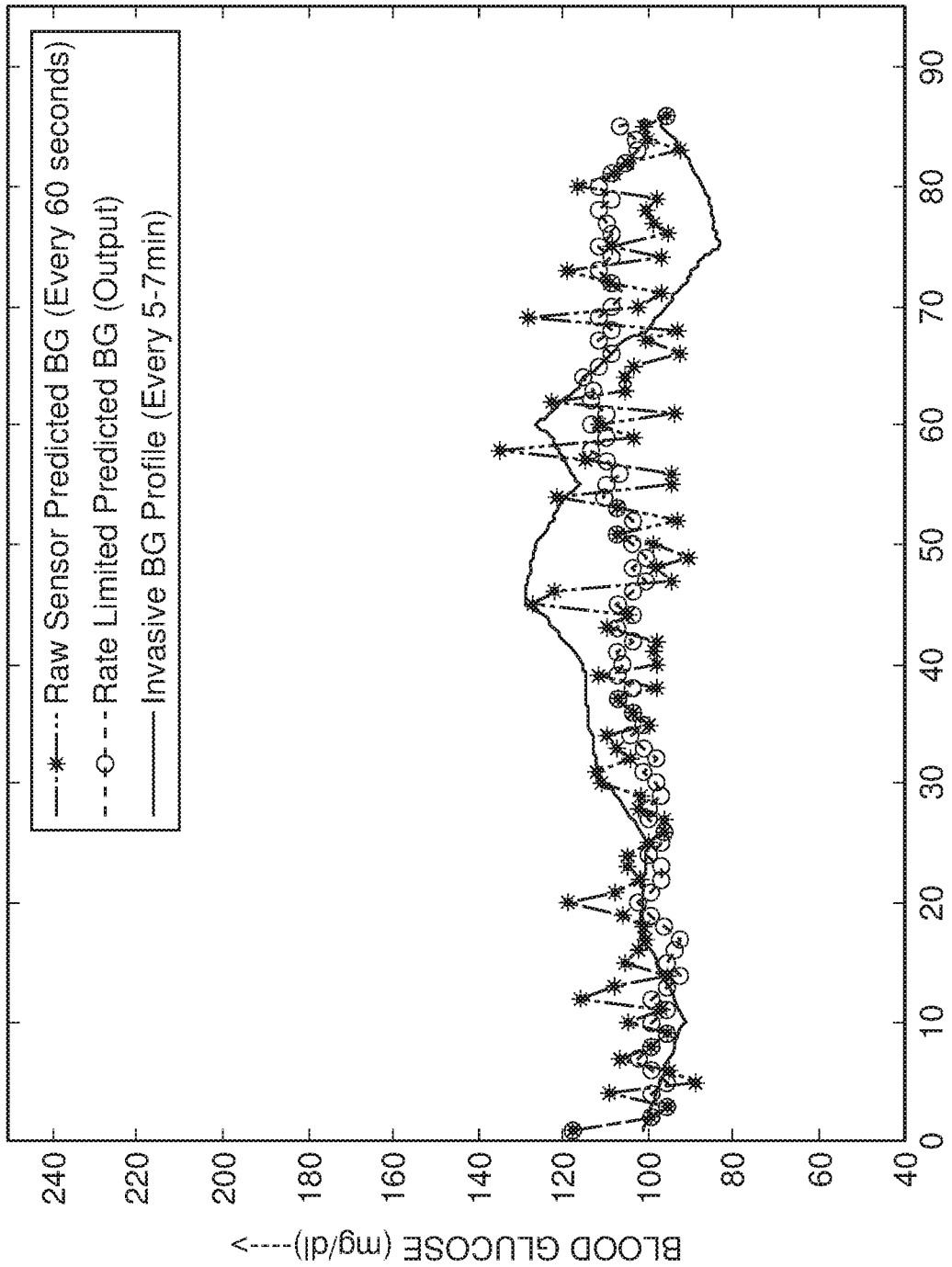
Raw Sensor Predicted BG (Every 60 seconds)
Rate Limited Predicted BG (Output)
Invasive BG Profile (Every 5-7min)
BLOOD GLUCOSE (mg/dl)---->
TIME (MINUTES)---->
240
220
200
180
160
140
120
100
80
60
40
0
10
20
30
40
50
60
70
80
90

FIG. 10

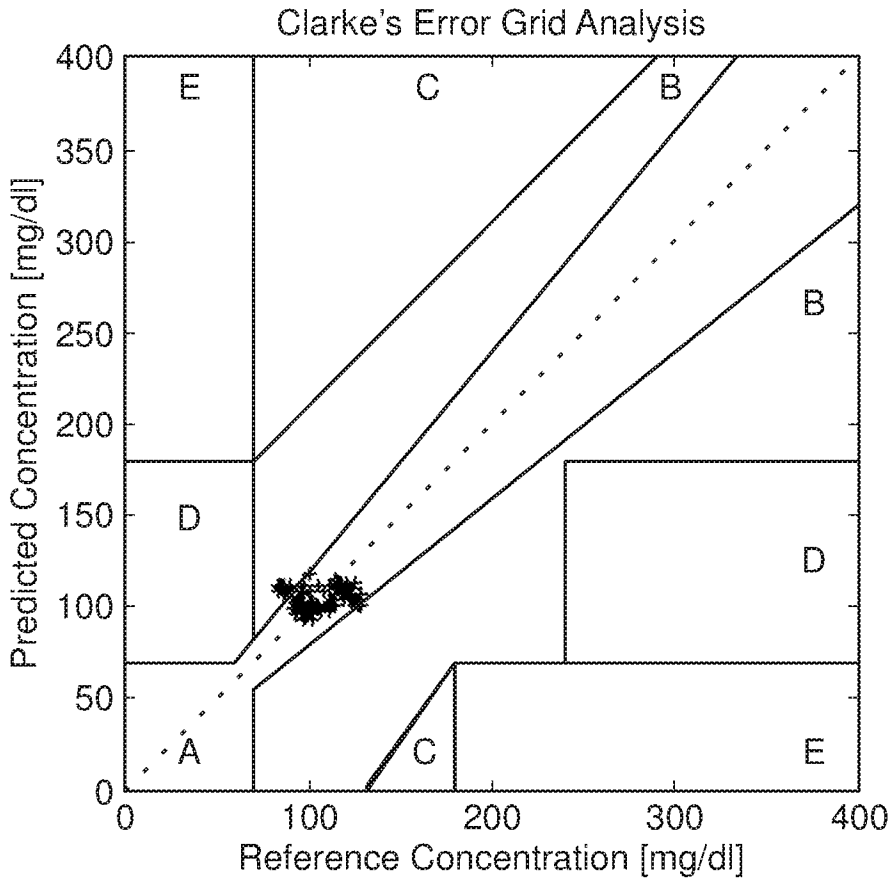
Clarke's Error Grid Analysis
Predicted Concentration [mg/dl]
Reference Concentration [mg/dl]
0
50
100
150
200
250
300
350
400
A
B
C
D
E

FIG. 11

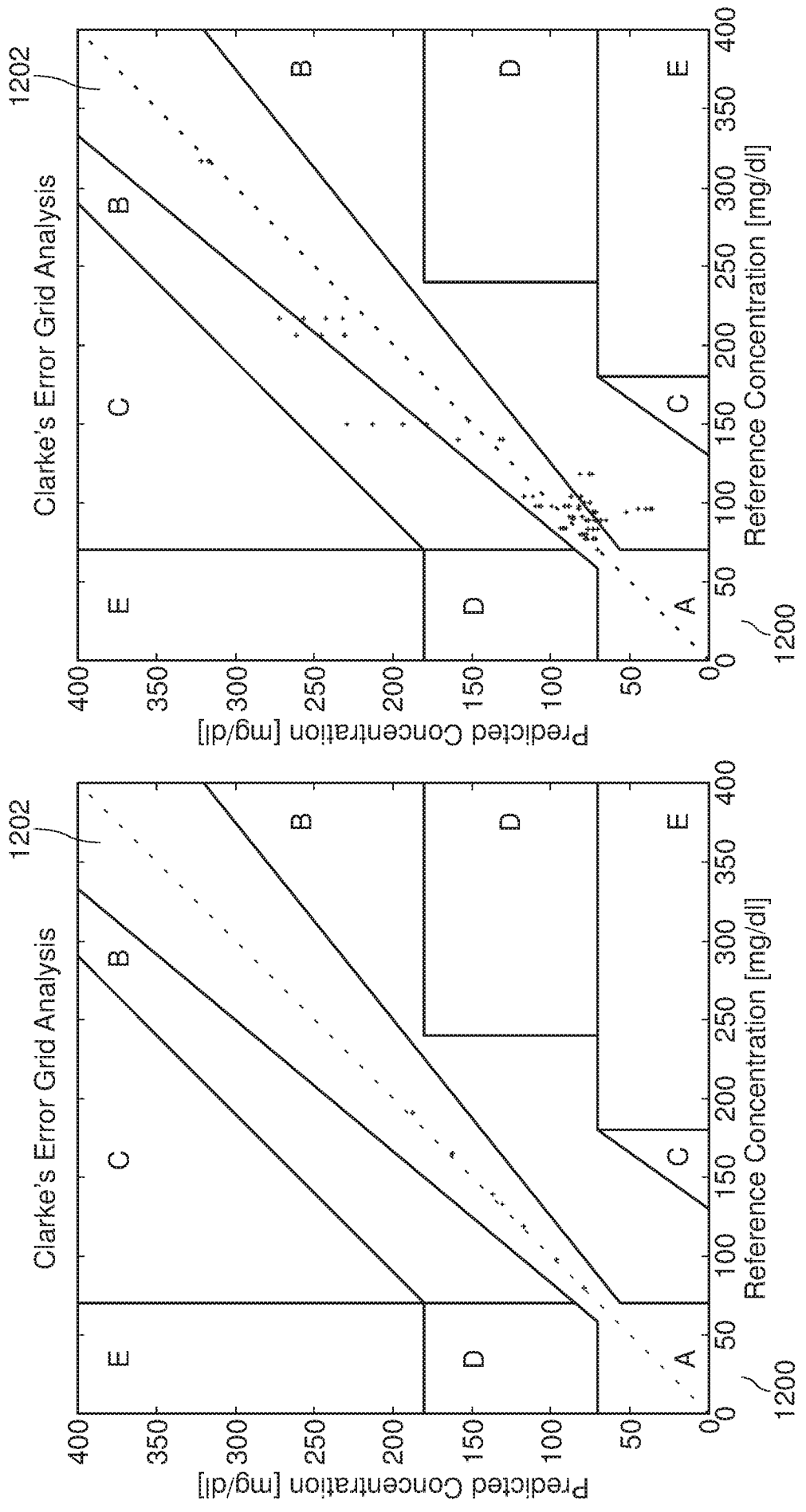
Clarke's Error Grid Analysis
1202
1200
Predicted Concentration [mg/dl]
Reference Concentration [mg/dl]
A
B
C
D
E
0
50
100
150
200
250
300
350
400
(a)
(b)

FIG. 12

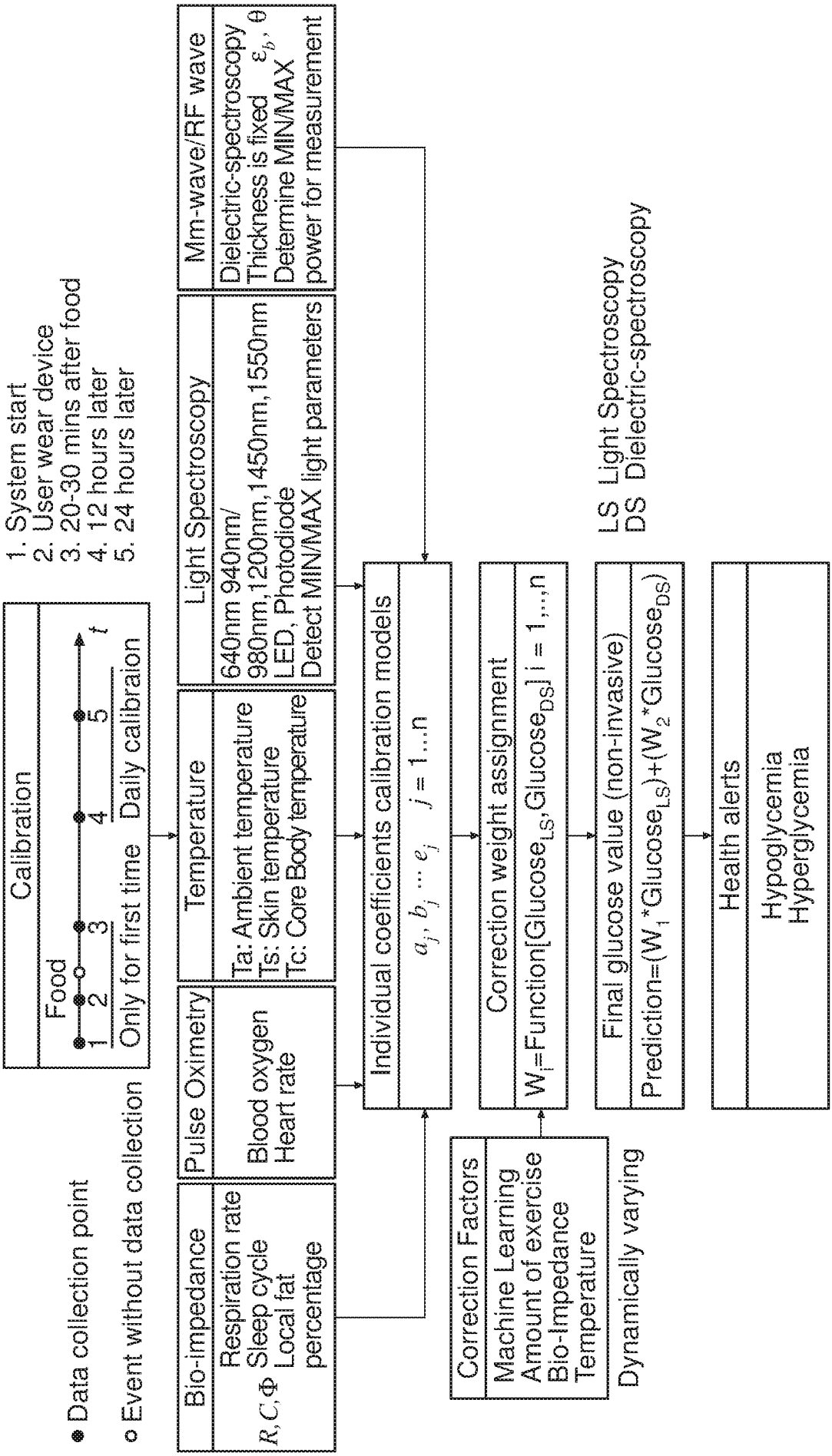
Calibration
Food
1 2 3 4 5 t
Only for first time
Daily calibraion
1. System start
2. User wear device
3. 20-30 mins after food
4. 12 hours later
5. 24 hours later
Data collection point
Event without data collection
Bio-impedance
Respiration rate
Sleep cycle
Local fat percentage
R, C, Φ
Pulse Oximetry
Blood oxygen
Heart rate
Temperature
Ta: Ambient temperature
Ts: Skin temperature
Tc: Core Body temperature
Light Spectroscopy
640nm 940nm/ 980nm,1200nm,1450nm,1550nm
LED, Photodiode
Detect MIN/MAX light parameters
Mm-wave/RF wave
Dielectric-spectroscopy
Thickness is fixed ε_b, θ
Determine MIN/MAX power for measurement
Individual coefficients calibration models
$a_j, b_j \cdots e_j \quad j = 1 \ldots n$
Correction Factors
Machine Learning
Amount of exercise
Bio-Impedance
Temperature
Dynamically varying
Correction weight assignment
W_i=Function[Glucose$_{LS}$,Glucose$_{DS}$] i = 1,...,n
Final glucose value (non-invasive)
Prediction=(W_1*Glucose$_{LS}$)+(W_2*Glucose$_{DS}$)
LS Light Spectroscopy
DS Dielectric-spectroscopy
Health alerts
Hypoglycemia
Hyperglycemia

FIG. 13

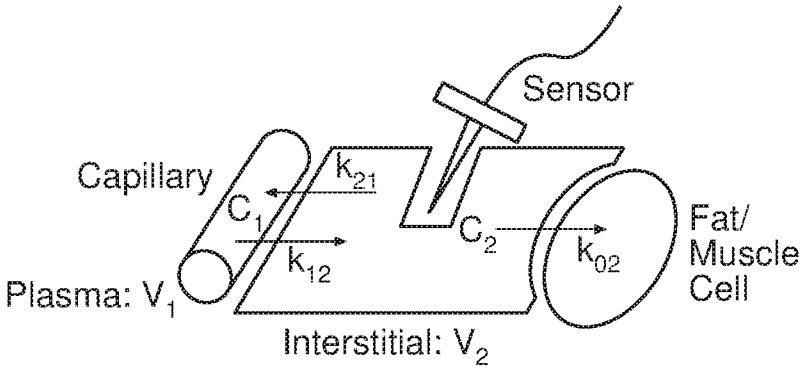
Sensor
Capillary
k_{21}
C_1
C_2
k_{02}
Fat/
Muscle
Cell
k_{12}
Plasma: V_1
Interstitial: V_2

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2015/050454

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/145 (2006.01) ***A61B 5/1455 (2006.01)*** ***A61B 5/1477 (2006.01)***

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

FAMPAT: blood glucose, wearable, radio-frequency, light spectroscopy, bio impedance, non-invasive

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/077260 A1 (BIOPEAK CORPORATION) 25 August 2005 para [0001], [0006], [0009], [0020], [0050], [0053]-[0054], [0056], [0059], [0061], [0067], [0070], [0088]-[0090], fig 1, 13, 21	1-26
A	WO 2010/062898 A1 (UNIVERSITY OF VIRGINIA PATENT FOUNDATION) 3 June 2010 Whole document, esp. pg 11 ln 2-4	-
A	WO 2007/053963 A1 (SOLIANIS HOLDING AG) 18 May 2007 Whole document, esp. pg 17 ln 30-36	-
A	WO 2009/152624 A1 (SOLIANIS HOLDING AG) 23 December 2009 Whole document, esp. pg 1 ln 26-33, pg 4 ln 27 – pg 5 ln 7	-

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25/01/2016 *(day/month/year)*	11/02/2016 *(day/month/year)*

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SG2015/050454

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		US 2009/0312615 A1	17/12/2009
WO 2009/152624 A1	23/12/2009	US 2011/0160554 A1	30/06/2011